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THE MEDICAL CLINICS OF NORTH AMERICA

SEPTEMBER, 1922

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W. B. SAUNDERS COMPANY

PHILADELPHIA AND LONDON

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CLINIC OF DR. ALBION W. HEWLETT

STANFORD UNIVERSITY HOSPITAL

PAROXYSMAL TACHYCARDIA. A CASE WHERE QUINIDIN LESSENED THE FREQUENCY OF ATTACKS

PAROXYSMAL tachycardia is characterized by the occurrence of attacks of rapid and regular heart action. These begin and end suddenly. During the attack the heart action is quite regular and the rate is usually between 140 and 220 per minute. The mechanism which gives rise to such attacks is in most instances a rapid and regular succession of abnormal auricular beats. The mechanism differs from that of auricular flutter: (1) because in flutter the auricular rate is more rapid, and (2) because in flutter there is believed to be a progressive circus contraction in the auricles and not a succession of complete auricular systoles.

The causes of paroxysmal tachycardia are but imperfectly understood. They are similar to the causes of extrasystoles, but we do not know why in the one case only occasional abnormal contractions take place, whereas in the other these recur in rapid succession. The paroxysms of tachycardia may be precipitated by exercise, emotion, strain, or posture; or again, they may start with no apparent cause. To avoid the recurrence of paroxysms an attempt is usually made to eliminate factors which are supposed to irritate the heart muscle. Tea, coffee, and tobacco are to be avoided and definite focal infections eradicated. Sometimes these measures seem to lessen the incidence of attacks. At other times the attacks disappear without treatment, particularly in young persons. Of medi-

cines that will lessen the frequency of attacks we know almost nothing. Usually it is difficult to demonstrate what measures influence the frequency of attacks, because the latter commonly recur only at considerable and variable intervals.

The following case is of interest because the attacks of rapid heart action recurred with great frequency and because this frequency was clearly lessened by the administration of quinidin.

Case report: Mrs. T. L., sixty-three years, was first seen April, 1921, complaining of attacks of palpitation. She was said to have had Bright's disease, with edema at twenty years, and to have had a recurrence at forty-five years. Complete recovery occurred after both illnesses.

The first attack of palpitation occurred forty years ago. At first these attacks recurred at intervals of several years. Gradually, however, the intervals became shorter. During 1920 she averaged at least one attack a week. In August, 1920 there were times when the attacks occurred daily. For the past ten days she has also been having daily attacks.

Her attacks always begin abruptly and without warning. Sometimes they come without apparent cause; sometimes they seem to be induced by hurrying upstairs or by fatigue. During the attacks she has a sense of throbbing about the chest and suffers some apprehension. There is no pain and no shortness of breath.

The attacks can usually be stopped by either of two methods. The first is pressure over the right vagus nerve. This is usually successful when executed by a physician, but she has not been able to perform it successfully herself. The second method of stopping the attacks is to induce vomiting by drinking salt water. In either case the attack terminates abruptly. Immediately after she feels well except for some prostration.

Examination showed that all teeth had been removed. The tonsils were not enlarged. The heart was very slightly enlarged on physical examination. The blood-pressure was 155/90. The urine showed occasional traces of albumin. The blood-count was normal.

The patient was observed during a paroxysm with a heart-rate of 190 per minute. This attack was stopped abruptly by pressure on the right vagus nerve, after which the heart-rate was 94 per minute. The electrocardiogram taken during the attack showed a rapid and regular ventricular rate. P waves were not definitely located. Immediately after the attack the mechanism was normal except for some left ventricular preponderance. The transition from the attack to the normal heart action was not recorded.

From April to June, 1921 the patient took, more or less continuously, the elixir of iron, quinin, and strychnin, 1 teaspoonful three times a day. The attacks occurred on the average of one in two days. This was somewhat less frequent than they had been previously, but the difference was not marked. From June 12 to June 27, 1921 she took 3 grains of quinidin sulphate three times a day, and during these two weeks she had only one paroxysm. Since that time, now over a year, the patient has had many opportunities to test the efficacy of quinidin. There have been times when she has discontinued it for weeks, always with the result that the paroxysms came more frequently. Reviewing her experience, she has recently stated that when she takes quinidin sulphate, 3 grains three times a day, the attacks of rapid heart action come, on the average, at intervals of three or four weeks; whereas, if she does not take the quinidin the interval is five days or less. The patient has become somewhat short of breath on exertion, but there is no noteworthy change on physical examination.

We have here a clear demonstration that in this patient quinidin sulphate in small doses lessened the frequency of attacks of paroxysmal tachycardia. In my opinion the continuous administration of the drug to this patient is justifiable, because frequent paroxysms of excessive tachycardia not only tend to unnerve the patient, but throw an additional strain upon the heart muscle. In the present case the drug was discontinued on several occasions, but the patient always requested its readministration.

CLINIC OF DR. THOMAS ADDIS

FROM THE MEDICAL DEPARTMENT OF STANFORD UNIVERSITY MEDICAL SCHOOL

PROTEIN RESTRICTION IN BRIGHT'S DISEASE

A LOW protein diet is usually prescribed for patients suffering from Bright's disease. It seems probable that this is sound practice, although it has no convincing experimental basis. When the kidney has failed to keep the concentration of non-protein nitrogen in the blood and tissues within normal limits there is, of course, a direct indication for a minimal protein intake. And even when, as in the great majority of cases, there is no accumulation of urinary nitrogen in the body, the conventional restriction of protein, with its consequent decrease in the work required of the kidney, can be defended on the ground that in acute or subacute inflammatory conditions, activity delays and rest hastens the processes of repair and ultimate cure. It is true that the validity of the application of this general principle to the special instance of renal disease has never been adequately tested even in those forms of Bright's disease which are clearly of an inflammatory nature. But, until evidence to the contrary has been produced, we are justified in assuming that the analogy holds true.

Assuming then that in Bright's disease it is right to reduce the protein in the food until no more is taken than will allow a safe margin over the calculated requirements for maintenance and growth, the question arises as to how this had best be accomplished in actual practice.

Experience, unfortunately, shows that there is no way of giving a low protein diet which is at the same time both simple and safe. It is a quantitative method of treatment, and attempts to apply it, which rely on such merely qualitative in-

structions to the patient as are comprised in giving lists of articles of food to avoid or to take, may have disastrous results. Further, it is a method which has no general applicability, but must be modified to meet the special requirements of each patient. The 2 patients I am presenting to you today illustrate the danger of an uncritical application of the method.

The first patient is a boy of nineteen years, who tells us that four months before his admission to the hospital he noticed a gradually increasing edema of the legs. There had been no preceding illness, and there were no subjective symptoms, but as the edema continued to increase he consulted a doctor. He was advised to take only milk, bread, butter, cereals, and fruit, and was treated very energetically with hot packs and cathartics. The edema at first decreased, but after about a month of this treatment it again began steadily to increase. On admission he was unable to move out of bed because of the enormous accumulation of fluid which involved all the subcutaneous tissues, had filled the peritoneal cavity, and had completely collapsed the left lung. The urine contained a very large number of casts. The count showed 12,354,000 in a twelve-hour urine collection. The great majority were hyaline casts studded with doubly refractile fat droplets. No blood-casts were ever found. The blood urea concentration was 31 mg. per 100 c.c., but the urea ratio test showed that only 38 per cent. of the average normal renal functional capacity was left. The blood-pressure was low and no other abnormalities beyond the colossal edema could be found. His condition corresponds to that described by Volhard and Fahr as "genuine" nephrosis.

From the point of view of treatment the most illuminating observation was the finding that he was daily losing large amounts of protein in the urine. The excretion in twenty-four hours varied from 11 to 34 grams and averaged about 20 grams a day. It thus appeared that he might well have been losing in the urine as much protein as he took in his food. Exact data as to his protein intake for the three and a half months preceding his admission could not be obtained, but it must have been quite low, as he had no appetite and took very little of the low

protein concentration foods which were given to him. It is clear that this diet, which was a low protein intake for anyone, amounted in his case to giving practically no protein at all. It had superimposed on a condition which in itself carries a tendency toward edema—the protein starvation edema which was observed so commonly in Europe during the war.

On a sufficient protein intake the edema gradually disappeared until today there is only a slight pitting around the ankles. It should be noted, however, that the giving of what some might call a "high protein" diet has had no effect on the nephrosis itself, for in every other respect than the edema he is now in the same condition as on entrance. High protein diets have recently been recommended for such cases on the ground that in some unexplained way the protein exerts a specific curative effect. There does not seem to me to be any justification for this view. To give a larger than usual amount of protein to a patient who is losing large quantities in the urine is simply to avoid an obvious error, and I have never seen any reason to suppose it is more than this.

The second patient is a boy of eight years who, in February of this year, developed generalized edema, hypertension, and nitrogen retention, with blood, albumin, and casts in the urine following a tonsillitis. I saw him a month later. The edema, hypertension, and nitrogen retention had gone, but the urine still showed evidences of a very active glomerular nephritis. The twelve-hour urine collection showed 2,160,000 casts, with a high percentage of blood-casts. Such findings are unusual a month after an acute glomerular nephritis in a child. The renal capacity was only 38 per cent. of the normal for a boy of his age. He had lost markedly in weight, was very apathetic, and had a −11 per cent. basal metabolism. For a month he had been on what was described as a "very restricted nephritic diet." In this case also there had been a loss of appetite, so that it seemed possible that the continued activity of the renal lesion, the apathy, loss of weight, and the rather low metabolic rate might in some degree at least be related to an insufficient protein intake. He was, therefore, given 2 grams of protein

per kilo body weight in an appetizing form and largely as animal protein. Within a week there was a noticeable clinical improvement and he began to gain weight. On April 21st his renal capacity had risen to 78 per cent. of the normal and there was a great decrease in the number of casts. In June the tonsils were removed. On July 19th the renal capacity was 96 per cent. of the normal and there were very few casts and only a trace of albumin.

There is nothing in either of these cases which can be taken as evidence against the assumption that it is right to give a low protein diet in Bright's disease. All that is shown is that in applying this method it is necessary to make allowance for protein lost in the urine, for the special requirements of growing children, and for the possibility that the diet which is ordered may not be taken. Simply to tell the patient to live on milk, vegetables, fruits, and cereals, without obtaining any accurate record of the amounts taken, may easily result in protein starvation, which there is every reason to believe is much more harmful to the patient than no dietetic treatment at all.

CLINIC OF DR. WALTER C. ALVAREZ

FROM THE GEORGE WILLIAMS HOOPER FOUNDATION FOR MEDICAL RESEARCH AND THE MEDICAL DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

DIAGNOSIS AND TREATMENT OF GALL-BLADDER DISEASE WITH SPECIAL REFERENCE TO THE MELTZER-LYON TEST

The Great Frequency of Gall-bladder Disease.—I would like first to call attention to the great importance of the subject which we are to discuss today. Statistics from many sources show that from 5 to 12 per cent. of all women coming to autopsy have gall-stones. If we exclude women under fifty the percentage is still higher. This alone would be surprising enough, but we know that there must be a still larger group of men and women in the community suffering from the precalculous stages of cholecystitis. There would seem, then, to be no escape from the conclusion that even careful clinicians are not making the diagnosis of gall-bladder disease often enough. I know I get the impression sometimes that I am becoming mentally warped on the subject because I suspect cholecystitis in every old lady who comes in with flatulence and abdominal pain; and then along come a few autopsies or operations on my patients, and I discover a number of gall-stones the presence of which I had not even suspected.

Now, how are we going to recognize a larger percentage of these cases, and what are we going to do for them?

The Meltzer-Lyon Technic.—As the Meltzer-Lyon method of so-called biliary drainage has been very much to the fore of late, I will take that up first. It will be remembered that in 1917 Dr. Meltzer,[1] one of the grand old men in physiology, put two hobbies of his together, and suggested, first, that inas-

much as the sphincter at the end of the common duct presumably must relax when the gall-bladder contracts, if the contents of the gall-bladder are to be extruded into the duodenum, then the activities of these two parts of the biliary tract must be co-ordinated and under the control of the "law of contrary innervation." Second, if this be true, magnesium sulphate, when it relaxes the smooth muscle of the papilla, must theoretically cause also a contraction of the gall-bladder. Third, magnesium sulphate injected near the papilla by means of a duodenal tube might have some influence in overcoming jaundice and biliary colic.

This last suggestion was immediately acted upon by Vincent Lyon who has been actively at work on the problem ever since.[2] He observed that when the tube is first put into the duodenum very little or no bile is present. Shortly after the injection of the magnesium sulphate, yellow bile appears, and then gradually there appears a darker and sometimes thicker bile. He decided that the first bile must come from the ducts and the darker bile must come from the gall-bladder. The next step was to diagnose cholecystitis by finding in the so-called "B" or gall-bladder bile, pus-cells, crystalline detritus, and bacteria. Furthermore, if the gall-bladder could be drained so perfectly in this way, what more natural than to assume that magnesium sulphate injections would clear up chronic infections of that organ.

On reviewing the large literature which has grown up about the subject in the last two years, one is struck by the fact that, as usual, the first men to rush into print with clinical papers have little besides success to report. Those more careful individuals who wait to see whether their cures are at all permanent always run the risk of coming in with their reports too late, that is, after the subject has died a natural death. A tremendous amount of research done on the problem will undoubtedly never be reported. Men do enough work to satisfy themselves that the method is unreliable and its therapeutic results are transient, and then they give it up. Even Lyon, judging by his last article,[3] has gotten into a less enthusiastic

mood. He admits now that prompt operation is the only treatment for frank, well-marked cholecystitis, and he disclaims any belief in "cures" of an "essentially chronic disease." The assumption of this more conservative position may be due in large part to the fact that practically all those who have done careful experimental work on the problem have shown there is little foundation for most of his views.

Physiology of the Gall-bladder.—In the first place, a review of the literature shows that there is now very little basis for Meltzer's original assumption that the law of contrary innervation holds in regard to the gall-bladder and the sphincter of Oddi at the lower end of the common duct. I need only point out that Meltzer was relying almost entirely on the experimental work of Doyon. That work was done with a rather crude technic, and it has since been quite discredited by the experiments of Bainbridge and Dale,[5] two of England's best physiologists. They excluded certain sources of error and got results exactly opposite to those of Doyon. A careful review of everything which has been written about the innervation of the bile-tract leaves me with but one strong impression, and that is, that the results of stimulating the nerves are so slight, so transient, and so variable that one certainly should not build any theoretic structures upon them.

Meltzer's original theorem has been still further discredited by the discovery that, although magnesium sulphate increases the flow of bile into the bowel, many other substances, such as sodium sulphate, sodium phosphate, hydrochloric acid, peptone, etc., do the same thing.[6, 7, 8, 9, 10] Furthermore, a number of these drugs give the typical color changes in the bile.[7] As it is well known that most of these substances do not relax the smooth muscle of the papilla, there is no basis for arguing that they will, by "contrary innervation," cause a contraction of the gall-bladder.

Meltzer's ideas have been discredited also by the failure of experimenters to demonstrate any considerable amount of contraction in the gall-bladder. In the first place, if it ever did empty itself we should expect quite frequently to find it

flabby or collapsed at operations on men or animals. Actually, we almost always find it full and fairly tense. Furthermore, it has been shown now by many writers that the gall-bladder is a weak and sluggish organ which never contracts like a urinary bladder even when it is stimulated directly by powerful electric currents. When it does contract it produces pressures of, at most, 30 mm. of water, barely enough to overcome the resistance of the valves of Heister in the cystic duct.[11, 12, 13, 14] I can find no evidence that the musculature is ever strong enough to overcome the pressures maintained ordinarily in the hepatic and common ducts (from 200 to 370 mm. of water). I have tried several times to stimulate the gall-bladders of animals into visible activity, but have never succeeded.

After reviewing the literature it is still a puzzle to me how and when the gall-bladder bile mixes with the duct bile, but it seems most probable that at meal-times, when the bile flows into the duodenum, a certain amount trickles out of the gall-bladder, not because the muscle there has contracted, but because the pressure in the ducts has been lowered. The muscle of the gall-bladder need then contract only enough to take up the slack in the wall.

Actually it has been shown at operations on men and animals that the instillation of magnesium sulphate solutions into the duodenum does not produce any appreciable contraction of the gall-bladder.[6, 8, 15] The objection may be made that the patient is under an anesthetic and that his abdomen is open, but it still seems to me, after years spent in demonstrating delicate gastro-intestinal reactions under just these conditions, that if the phenomenon is as definite as it has been supposed to be, it should be demonstrable even under somewhat adverse circumstances. Besides, Okada[9] states definitely that, with balloons inserted through gall-bladder fistulæ, he obtained better contractions in anesthetized animals than in unanesthetized ones. Similar observations were made by Mann.[16]

In view of these findings it is clear that Lyon can no longer proceed on the assumption that the "B" bile comes from the gall-bladder. There are only a few experiments recorded which

suggest that occasionally that may be the case. Most of the experiments show conclusively that the color changes can be obtained in the entire absence of a gall-bladder, *i. e.*, when that organ has been removed by operation or closed off by disease.[6, 7, 17] In one case reported the usual "B" bile was obtained, but next day at operation the cystic duct was found absolutely closed and the gall-bladder filled with bloody pus.[7] In other experiments methylene-blue was injected into the gall-bladder by means of a hypodermic syringe, and although the Meltzer-Lyon technic repeatedly brought out considerable "B" bile, no methylene-blue appeared in the duodenum.[6] Another objection to the technic is that the test can be repeated several times at intervals of three-quarters of an hour, there being obtained at each pumping considerable amounts of "B" bile.[8] If the gall-bladder were to empty itself thoroughly the first or even the second time this could hardly happen.

It follows from all this that if we cannot assume that the "B" bile comes from the gall-bladder, we must not diagnose cholecystitis simply because we find some bacteria in that bile. Furthermore, it would be very unwise to draw any conclusions about bacteria obtained through the duodenal tube in view of the fact that the duodenum, even in the presence of a normal gall-bladder, is rarely sterile.[18, 19] A review of the literature on the subject shows that the number of bacteria found will probably depend more on the amount of hydrochloric acid in the gastric juice,[20, 21] the length of time after eating,[22] the degree of sterility or infection of the last food eaten,[23] the condition of the teeth, the amount of saliva swallowed, etc., than on the condition of the gall-bladder.

Another big difficulty is that in a surprisingly large proportion of the cases of gall-bladder disease operated upon no bacteria can be grown from the bile even with the most advanced cultural methods. This has been my experience, and it is the experience of many others. Even in the presence of stones, the chances are more than even that the bile will be sterile.[23, 24, 25, 26, 27] Years ago I got the idea that the microscopic examination of a few drops of bile removed at operation through a fine needle

might help the surgeon in deciding whether or not to take out a questionable gall-bladder. A few experiments along this line soon showed me that this hope was ill founded. The bile specimens were surprisingly normal even in the presence of definite disease. If my simple test was doomed to failure, how much less chance must there be for one in which the bile is contaminated and of uncertain origin!

It seems pretty clear, then, that, as a diagnostic procedure, the method has hardly a leg to stand upon. A little later we will take up its therapeutic pretensions to see whether they can emerge in any better shape from a similar critical analysis. For the moment, having pointed out how *not* to make a diagnosis of gall-bladder disease, I would like to discuss briefly the points which I think *are* helpful.

A Good History.—In the first place, we must get a good history. The longer a man practices and the better clinician he becomes, the more he will depend upon the careful study and appraisement of symptoms. Cases that seem at first to be puzzling and obscure often become quite simple when the patient is made to recall some attacks of supposed ptomain-poisoning which had all the earmarks of gall-stone colic. The experienced physician knows that recurrent attacks of severe pain which perhaps waken the patient out of a sound sleep and which leave her upper abdomen sore for days afterward must be due to organic disease; they cannot be ascribed to a neurosis or to slight indiscretions in diet.

Although we must be particularly on the lookout for cholecystitis in women between forty and sixty-five, it must be remembered that the disease does occur in men, and, as our experience grows, we are going more and more to recognize the early stages in young people and sometimes even in children. We know from the histories which we take that the disease often must begin in childhood and youth; the next thing to do is to learn to recognize it when we see it.

In the most typical cases the pain begins in the liver region and runs into the back and up into the right shoulder-blade. In early cases the main complaint may be of a constant aching

under the right lower ribs. The soreness is aggravated by riding over a rough road or by reaching for a high shelf. Women perhaps will be unable to bear the pressure of their corsets in the liver region. In milder cases and in the intervals between attacks the patients complain mainly of belching and bloating. They often feel "bilious" and get a little sallow. Only rarely are they jaundiced, and the physician must not depend on that symptom. Nausea, regurgitation of food, and heart-burn are common. Vomiting often comes during attacks of pain.

Most characteristic and helpful is the patient's statement that although she has a fine appetite *she is afraid to eat;* she *so* dreads the return of pain. Yet she will admit that what she eats seems to have little or nothing to do with the bringing on of an attack. She may get a bad one after a week of fasting, and later she may digest a Thanksgiving dinner without discomfort.

Many of these people have suffered so much that they have gladly submitted to one or more operations. Too often, however, to my great regret, the surgeon has contented himself with the removal of a normal appendix through a tiny gridiron incision, the smallness of which, while conducive to his vanity, precluded any efforts at a thorough exploration of the abdominal cavity.

A history of typhoid fever, chronic sinusitis, empyema, or any other severe and prolonged infectious process is helpful because such things often leave the gall-bladder damaged irreparably.

The presence of arthritis, myocarditis, and certain forms of headache and dizziness is suggestive because these troubles sometimes clear up after cholecystectomy.

The Physical Examination.—The most suggestive finding is a tender liver edge; and in many cases the diagnosis can easily be made if the patient has a definitely positive "Murphy's maneuver." The hand is thrust as far as possible under the ribs on the right side; the patient takes a deep breath, and as her liver comes down against the examiner's fingers she gives a start and a gasp of pain. The presence of fibroids in the

uterus or other pelvic abnormalities greatly increases the probability of finding gall-bladder disease.

Roentgen-ray Examination.—This can help greatly in several ways: First, it may exclude the presence of other organic lesions, such as ulcers and carcinomas. Second, it may show the shadow of stones or of a thickened gall-bladder on the plate. Unfortunately, most of the diseased gall-bladders are free from stones and so thin walled that they will not show on the plate. Furthermore, many stones are too soft to give a shadow. Third, the screen examination often shows many suggestive things. Cardiospasm is often seen, and I am coming to think more and more of it as an indicator of gall-bladder disease. The stomach is often hypertonic and overactive, and not infrequently the pyloric antrum is contracted and sharply conic in shape. There may be some gastric stasis, and it may also be apparent to an experienced observer that the gastric mucosa is dry (achyliac). The duodenal cap is sometimes deformed by adhesions or pressure, and it may also show defects in emptying. The colonic haustration is often exaggerated. The liver is not infrequently enlarged from the cirrhosis attendant upon prolonged infection of the bile-ducts.

Laboratory Tests.—Gastric analysis may be helpful if it shows an achlorhydria, since a lack of hydrochloric acid is commonly found with gall-bladder disease.

Treatment.—Like appendicitis, gall-bladder disease may go on and kill the patient, or it may clear up even without treatment. Once cleared up, it may leave the victim alone, or it may come back at intervals until, finally, something has to be done. We know now that it is best and safest to take diseased appendices out. Unfortunately, we do not know yet what to do with the early cases of gall-bladder disease. If we could only look into the future for the different individuals it would be easy. When I see women about sixty-five, emaciated, worn with suffering, anxious for an operation which they cannot well stand, I tell myself that it is my moral duty to urge the younger ones to go to the surgeon. When, however, I see a series of women about forty who have gone ten or fifteen years without

attacks or much distress, I waver, and am inclined, as is the patient, to let well enough alone.

Unfortunately, it seems impossible to say when these people are really "cured" and free from the menace of their diseased bile-tracts. Thus, one would think, after several attacks of gall-stone colic that an interval of twenty years without troublesome symptoms would indicate a cure, but I have seen a woman in whom such a period of relief was really only an interlude. When she was sixty-one her troubles returned; a plate showed that a stone still remained, and an operation showed that a carcinoma had developed somewhere in the biliary tract.

It is hard to say whether medical treatment does much good because remissions occur so frequently and come so suddenly. Ordinarily it is well to advise a smooth, cellulose-poor diet, that is, without salads, coarse vegetables, or fruits. Some people are helped by the taking of Carlsbad salts in hot water before breakfast. Belching and heart-burn are often helped by the giving of sodium bicarbonate and magnesia. Hoffman's anodyne often brings relief during attacks at night. During paroxysms of pain paregoric, morphin, and papaverin have to be used. The physician should remind the patients who are losing weight that they will probably have trouble whether they eat or not, so that they had better eat and keep their strength.

A Classification of Cases for Treatment.—For therapeutic purposes the cases may at present be divided into six or seven groups. Medical treatment should be reserved for:

First: Those who are in the early stages of the disease, with mild symptoms and long intervals of relief, whose bodies are still young and strong, and who may perhaps yet hope permanently to overcome the infection.

Second: Those whose symptoms and findings strongly suggest the presence of cholecystitis, but who are suffering so much from nervousness, menopausal storms, hypertension, or myocarditis that it is a question whether they would be any better off even if a markedly diseased gall-bladder could be removed safely. These people must be studied carefully before any decision is made in regard to operation.

Third: Those who need and want an operation, but who, on account of complications, cannot undergo it with any prospect of success.

Fourth: Those who have had a cholecystectomy, but who still suffer. Many of these people might have gotten a perfect result if they had been put on a smooth diet after operation.

In the absence of definite contraindications operation should be advised for:

First: Those who have reached that stage of the disease in which the attacks are getting steadily worse and more frequent.

Second: Those whose indigestion is severe enough to interfere with their ability to work and to enjoy life. They should be the more willing to accept operation if they have an arthritis, headaches, dizziness, or myocarditis which may perhaps be cured by the removal of the infected gall-bladder.

Third: Those who have had their gall-bladders drained and who have gotten relief, but who now return with pain and perhaps with new stones.

Finally, and this is a most important point, the surgeon must be willing to admit that at the time of operation he cannot tell a diseased from a normal gall-bladder. Men of experience know that not infrequently gall-bladders which, according to the history, must have been discharging stones off and on for twenty years, are found at operation to be still soft and apparently normal. If they were not full of stones the surgeon would generally pass them by as innocuous. This does not mean that I am arguing for the reckless removal of gall-bladders. Far be it from me, but, as Judd says, there is no doubt that in many cases if the patient is to be helped his gall-bladder must be removed on the strength of a careful history taken by an experienced man. This removal can be done with more confidence if there are no other signs of disease in the abdomen to explain the severe symptoms, and if there are adhesions about the gall-bladder, an enlarged gland near the cystic duct, an enlarged liver, and signs of perihepatitis and pancreatitis. I am convinced that the poor results obtained in many of the cases of operative interference for duodenal ulcer can be ascribed

to the leaving behind of gall-bladders which had become badly involved in the inflammatory process about the bowel.

The Therapeutic Side of the Meltzer-Lyon Procedure.—Now, when are we going to use the Lyon method of drainage, and what can we reasonably expect it to do now that we have given up any hope of its really squeezing and emptying the gall-bladder? What can we hope to do when, as so often happens, the bile is normal and the infectious process is scattered through the walls of the gall-bladder and the bile-ducts up into the liver and down through the glands on the cystic duct into the head of the pancreas?[27, 28, 29, 30] Even if we could clear up the infection with a few treatments, could we prevent its recurrence? Why should the "non-surgical drainage" succeed when the surgical drainage so often has failed?

Basic Principles Underlying the Development of Cholecystitis.—At the Hooper Foundation in San Francisco Dr. Meyer[31] has shown clearly that the gall-bladder wall shares with the liver the remarkable function of rapidly removing bacteria from the blood-stream. Not infrequently it gets so damaged in the process that it either remains as a focus of infection or else becomes an area of minor resistance, subject to invasion by every bacterium that comes along by way of the blood-stream. Meyer has produced chronic recurring cholecystitis in animals simply by putting small foreign bodies into their gall-bladders. This little handicap so lowers the resistance of the organ that although it may clear itself of infection from time to time, it cannot stay clear. Similarly, a woman with gall-stones or a scarred gall-bladder is subject to a flare-up of infection whenever she has a cold or whenever she puts undue strain upon her digestive tract.

That being the case, it seems to me there is only one thing to do with a gall-bladder which is handicapped by the presence of stones or the scars of previous disease, and that is, to take it out. That is the opinion of the best surgeons of the land—men who have learned the futility of medical treatment and the danger of leaving behind bladders which have been drained. We cannot expect the Lyon technic to affect stones when they

are present. We can perhaps expect it to help in the clearing up of infectious jaundice. I agree with Lyon that it is worth trying in many of the cases in which surgical help must be postponed or refused.

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THE MANAGEMENT OF DIPHTHERIA

THERE is no disease in which the successful management has been so thoroughly developed and the gross mismanagement so often practised as in diphtheria. If one is inclined to doubt this rather sweeping statement he need only consult the mortality records of the United States for any year since 1904 to learn that from 15,000 to 20,000 deaths occur in this country annually from diphtheria. This rather startling status seems almost incredible and is, to say the least, a sad commentary on medical knowledge and medical education. With a full realization of the tremendous number of lives that are lost on account of the carelessness of parents and their disinclination to summon medical advice until the disease has reached a stage where it is no longer curable, one is confronted constantly with instances where lives might have been saved had the situation been more radically grasped by the medical man in attendance. In this connection two very startling facts stand out, both of which play a tremendous rôle in this high mortality rate. First, the delayed administration of antitoxin, and second, the improper administration of antitoxin. It is difficult to determine which of these two fundamental errors is the more detrimental, but an analysis of cases suggests very strongly that delayed administration is responsible for the greater percentage of deaths. In an effort to account for this deplorable situation one is forced to the disagreeable conclusion that the average medical student graduates with a very poor knowledge of the clinical phases of diphtheria,

because he considers himself fortified by what he has learned in the bacteriologic laboratory. There is no disease in which the capacity to apply laboratory findings is more important. On the other hand, from a prognostic standpoint, nothing can be more sinister than the utter disregard for clinical symptoms in view of negative bacteriologic reports. In contrast to this rather discouraging attitude of the inexperienced practitioner, more seasoned medical men are inclined to ignore the problems associated with a more comprehensive study of the actions of toxin and antitoxin, and to content themselves with the assurance that all obligations toward their patients are fulfilled if the directions handed out by commercial biologic laboratories are accurately followed. A consideration of a few clinical problems may serve to justify this rather cynical attitude.

Case I.—M. V., female aged four years, admitted to the Children's Hospital November 16, 1921.

Family history negative.

Previous History.—Has had attacks of "croup" at least twice before. Has never had antitoxin previously. Gives no history of asthma, eczema, urticaria, or other symptoms of protein hypersensitiveness.

Present Illness.—Three days before admission (November 13, 1921) child seemed slightly indisposed and had a loose cough. Her mother looked at her throat and discovered a small white spot on one tonsil, which she swabbed with iron and glycerin. During the night the patient was somewhat croupy, but this was promptly relieved by the application of a mustard plaster. The following morning the mother was no longer able to see any white spots on the tonsil, but the cough persisted, the breathing was somewhat labored, and the hoarseness quite marked. The administration of syrup of ipecac induced vomiting, which relieved the hoarseness greatly. The following day, November 15, 1921 (two days after onset and one day before admission to the hospital), patient seemed better, but toward evening became hoarse, and during the night this hoarseness increased very much and the cough was

frequent and troublesome. On the day of entry patient awoke feeling very ill. She complained of epigastric pain and vomited. She continued very hoarse, although she did not lose her voice completely. Patient was first seen on the evening of November 16, 1921, three and a half days after the onset of illness, at which time it was learned that she had been examined by her family physician earlier in the day, and, finding an exudate on the tonsils, he had taken a culture, deferring further treatment, notwithstanding the aphonia, until he could avail himself of the laboratory report on the following morning.

Physical Examination.—Patient is a well-nourished girl of four years. She does not appear very ill. Her color is good and she is not prostrated. Temperature, 100.4° F. Pulse, 120. Her voice is very husky, but there is not complete aphonia. The cough is more nearly aphonic than the voice. A slight mucoid discharge is present from the nose, but no membrane is apparent. The tonsils are enlarged and edematous, and scattered over the surface of each are small patches of grayish-white membrane, situated to a great extent in the follicles, the type of diphtheric exudate to which the adjective "herpetiform" is sometimes applied. The membrane does not extend at any point either to the pillars or on to the walls of the pharynx. The uvula is slightly edematous. The cervical glands at the angle of the jaw are moderately enlarged. The physical findings are otherwise essentially negative.

Hospital treatment was advised, and patient was admitted to the Children's Hospital with a clinical diagnosis of tonsillolaryngeal diphtheria. She was immediately desensitized by the intramuscular injection of 1 c.c. of antitoxin. One hour later she was given 1 c.c. of antitoxin intravenously, and after the lapse of another hour she received an intravenous injection of 10,000 units. No reaction occurred. Twelve hours after the administration of the antitoxin the temperature was definitely lower and the general condition of the child considerably improved, although the hoarseness persisted and the membrane had not changed either in character or extent. Cultures taken from the throat showed Klebs-Löffler organisms. The urine

showed a trace of albumin, but was otherwise negative. By the following day (thirty-six hours after treatment had been instituted) the membrane had practically disappeared and the temperature was normal. The degree of hoarseness was distinctly less. During the following forty-eight hours the voice became normal and the child presented no unusual symptoms. The urine, however, continued to show a trace of albumin and an occasional hyaline cast for several days. Three negative cultures having been obtained, and physical examination revealing nothing abnormal in either the heart, kidneys, or nervous system, the patient was allowed to go home eleven days after entry to the hospital, with the strict understanding that she was to be kept absolutely quiet in bed. She was seen at home repeatedly and, to all intents and purposes, her heart action was excellent. A very careful scrutiny of her reflexes, palate, and accommodation apparatus showed no evidence of nerve involvement, so that one week later her mother was instructed to lift the child very carefully and allow her to sit up in a chair half an hour. The next two days she was allowed to sit up one hour and two hours respectively. On the following day, exactly three weeks after her antitoxin had been given, the child suddenly complained of nausea, epigastric pain, and slight giddiness. On examination her pulse was found to be somewhat rapid (110), and the heart sounds suggested at least a tendency toward embryocardia. Aside from a slight pallor there was nothing remarkable in her general appearance. She was again put at complete rest and on a liquid diet for twenty-four hours. Opiates were not required. At the end of seventy-two hours her unusual symptoms had disappeared. The little girl was kept entirely in bed for three weeks after the development of her cardiac disturbance, at the end of which time she was very gradually allowed up, and in the course of two months had apparently made a complete recovery.

Case II.—M. M., female aged six years. Admitted to Children's Hospital February 5, 1922.

Family history negative.

Previous history was also negative except for a recent attack of influenza. Has never had any previous injection of serum. Has never developed any symptoms suggesting protein hypersensitiveness.

Present Illness.—The onset occurred forty-eight hours before admission to the hospital, February 3, 1922, when patient was taken suddenly ill in school with a chill followed by high fever, as a result of which she was sent home. The mother, believing that the child had a slight cold, purged her and kept her in bed. The following day, the patient being still ill and having complained of sore throat, the family physician was called. He announced that he was suspicious of diphtheria and called a children's specialist on the case. The pediatrist, after his examination, told the mother that the tonsils were very much enlarged and that he believed them to be abscessed. He accordingly turned the child over to a throat specialist, who made a diagnosis of quinsy, and incised the points of greatest edema on both sides without evacuating any pus. For some unexplainable reason cultures were not made. The child continued to grow rapidly worse, and on the next day a telephonic communication was received by the Children's Hospital from the mother, who stated that she feared that her child had diphtheria and wished to have cultures taken to confirm or disprove her suspicions.

Physical Examination.—Patient is a poorly nourished, desperately ill looking girl of six years. She lies in bed with her mouth held open and her head hyperextended, bringing out more forcibly the tremendous swelling of the cervical lymph-nodes on both sides. Her respiration is distinctly stertorous, her voice thick, but not aphonic, and there is a marked grayish subcyanosis of the skin, especially about the mouth. The breath has a horribly sweetish, putrid odor. The mentality of the child is profoundly affected and she is barely conscious. The pupils are widely dilated and there is a slow oscillation of both eyes. Both tonsils are enormously swollen and edematous so that they nearly meet in the midline. This edema extends to the pharynx and palate. The tonsils, pharynx, and palate are covered with a thick, grayish membrane which extends over the palate nearly

to the incisor teeth, the whole back of the throat being literally plastered with membrane. The glands at the angle of the jaw are very greatly swollen and the adjacent tissues are tremendously edematous, producing a collar-like effect encircling the neck. The heart is situated on the right side of the body and, aside from a tachycardia, is essentially negative. There are a few scattered coarse, moist râles throughout both lungs. The remainder of the physical examination shows nothing noteworthy. Temperature, 101.8° F. Pulse, 128. Respiration, 28.

Treatment.—Patient was immediately given 1 c.c. of antitoxin intramuscularly and one hour later 1 c. c. intravenously. At the end of the next hour, no reaction having been produced by the small intravenous dose, an attempt was made by the house officer to give the full dose of 10,000 units intravenously. She did not succeed, however, in entering the vein, probably on account of the marked circulatory failure, and, accordingly, gave 40,000 units intramuscularly. One hour later, in view of the very profound toxemia and realizing the hopelessness of the prognosis, a second attempt was made to administer antitoxin intravenously, and 7000 units were successfully given by the intravenous route. No reaction occurred to the antitoxin. During the next twenty-four hours the patient improved somewhat, the temperature dropped to 100° F., and the child seemed brighter, although the pulse remained rapid and the grayish color persisted. The swelling of the neck had subsided very markedly. The laboratory reports showed the presence of diphtheria bacilli in the cultures. The examination of the blood showed hemoglobin 80 per cent., white blood cells 28,000, with 85 per cent. polymorphonuclears. The urine showed a great deal of albumin, a trace of diacetic acid, and numerous granular casts. At the end of forty-eight hours the child's condition was much improved, her color was better, although still grayish. The glands were rapidly subsiding and the membrane had nearly disappeared, together with the edema and swelling of the affected tissues. The pulse continued rapid (100–120) and was at times weak and compressible. During the remainder of the first week after treatment the child continued to improve, the membrane com-

pletely disappeared, and the cervical gland enlargement subsided. There was some sloughing of the tissues around the incisions that had been made following the erroneous diagnosis of peritonsillar abscess. The pulse dropped to 90 to 100, was still easily compressible, and the color continued rather grayish. The heart sounds were weak, but otherwise showed nothing striking as to rate of rhythm. Seven days after receiving her antitoxin the patient developed a typical urticarial serum rash which disappeared in forty-eight hours. The urine on repeated examinations continued to show considerable albumin and numerous hyaline and granular casts, with many red blood-cells. The child was kept at absolute rest, no exertion whatsoever being allowed. On February 13, 1922, eight days after entry, ten days after the onset of her illness, the child vomited and complained of nausea and slight epigastric pain. Her color became bad and she developed a marked grayish pallor. The pulse was very soft and compressible and the heart sounds faint and muffled. The rhythm became embryonic in character. During the next forty-eight hours the child's condition was very grave. She was exceedingly restless, which restlessness was controlled by the frequent use of codein hypodermically. The pulse was soft and compressible, the heart sounds fetal in type, and very faint, although a heart-block of sufficient degree to show characteristic auscultatory changes was not apparent. The color, especially about the mouth, was typically subcyanotic. Forty-eight hours later, on the fifth day after the onset of what seemed to be fatal symptoms, although her condition was still precarious to the extreme, the child began gradually to improve, her restlessness diminished, her color improved, the heart sounds were of better character and assumed a more nearly normal rhythm, and the pulse became fuller and of better quality. The albumin and the casts in the urine gradually diminished. Her reflexes remained normal throughout this stormy period. During the next few weeks she continued gradually to improve, her pulse grew stronger, her color became normal, and, having become in the meantime culture free, she was discharged from the hospital March 14, 1922, thirty-eight days after entry, with

the understanding that absolute bed rest would be enforced at home, as it had been in the hospital. On the morning of discharge it was first noted that her knee-jerks were markedly diminished, although the other reflexes—papillary, pharyngeal, and tendon—were normal. The following day the knee-jerks were absent and the voice was nasal in character. There was demonstrable a complete palatal paralysis. The eyes were apparently unaffected. Twenty-four hours later the paralysis had further advanced to involve the respiratory muscles on the right side of the thorax and the abdominal reflexes on the same side were appreciably diminished. Coincidental to the appearance of these untoward manifestations the heart-rate was again accelerated and the color subcyanotic, although the circulatory disturbances were far less pronounced than previously. The neurologic symptoms fortunately progressed no further. In forty-eight hours the heart action was tremendously improved, the pulse strong, the color much better, and the slight respiratory paralysis had completely disappeared. The palatal paralysis was no longer demonstrable at the end of three weeks, about nine weeks after the onset of the illness, and two weeks later the knee-jerks were normally active. By the middle of April, about eleven weeks after the onset of her illness, the little girl was allowed to be out of bed, sitting up in a chair a gradually increasing length of time each day. She was not allowed to walk until the time interval of sitting up in a chair had reached six hours, when her exercise was gradually increased. On May 15, 1922, about fifteen weeks after the onset of her attack of diphtheria, she was discharged as completely cured.

Case III.—W. K., male aged six years. First seen at home January 15, 1922 at 9 P. M.

Family and *previous histories* were unessential.

Present Illness—On the previous day, January 14, 1922, patient had been perfectly well. In the evening, however, twenty-four hours before being seen, he became feverish and did not seem well, although he was not very ill. He was given a laxative by his mother and had a fairly good night. In the

morning and during the day, although he played around, he was rather listless, but complained of no pain until late in the afternoon, when he developed a sore throat. An examination of the throat by his mother revealed the presence of white spots, as a result of which medical advice was sought immediately.

Physical Examination (9 P. M. January 15, 1922).—Patient is a very well-nourished boy of six years. He does not appear very ill and is not apparently uncomfortable. The tonsils are considerably enlarged and covered with exudate on both sides. This does not extend off the tonsils at any point and is not continuous over their surface. The uvula is rather succulent looking, but there is very little swelling or edema of any of the tissues. The cervical glands are discretely swollen at the angle of the jaw. Physical examination is otherwise negative. Temperature, 103° F. Pulse, 136. The general impression that the case gave in view of the high temperature and the location of the exudate was that of a streptococcus tonsillitis. Cultures were made from the exudate and material obtained upon sterile swabs for the immediate examination of direct smears. They were stained by the Gram method and with Kinyon's stain. The Gram stain specimen showed Gram-positive rods with the typical general morphology and grouping of Klebs-Löffler bacilli. The Kinyon differential stain showed typical polychromatic granules. In view of the short duration of the case, the mild toxemia, and the small amount of membrane it seemed good judgment to administer the antitoxin intramuscularly instead of intravenously. He was accordingly desensitized at midnight with 1 c.c. of antitoxin intramuscularly, and at 1 A. M. given 30,000 units intramuscularly into the gluteus muscle. No reaction occurred. The patient was seen the following morning at 9 A. M., approximately thirty-six hours after the onset of his illness, exactly eight hours after the injection of his antitoxin. The picture was shockingly altered. The child looked desperately ill. His color was ashen gray and his lips subcyanotic. He was semidelirious and fought examination wildly. The throat was tremendously edematous, the tonsils swollen nearly to the midline, and the uvula was swollen almost sufficiently to block the remaining space. The

exudate had extended on to the anterior pillars and the posterior wall of the pharynx was nearly covered with exudate. The cervical glands were enormously swollen and the regional tissues edematous. The temperature was 102° F. and the pulse 148. By noon, three hours later, about eleven hours after he had received his antitoxin, there was slight but definite improvement. The pulse had dropped to 136 and was of better quality. The color was, however, still bad and his condition a source of concern. At 4 o'clock, fifteen hours after his antitoxin injection, he was very definitely improved. He had developed a distinctly pink hue to his skin, his heart action was stronger, and the pulse had dropped to 130. During the early evening he seemed exhausted, but rested comfortably. Later during the night he was again delirious. The following morning, about thirty-two hours after he had received his antitoxin, the child seemed much better. His color was good, pulse 120, and his heart action was excellent. He was fully conscious and took his nourishment well. His temperature gradually dropped and reached normal the following morning, fifty hours after the injection of his serum. Coincidental with this improvement in his general condition there was a marked recession of all of the local signs. The swelling and edema had practically disappeared and the membrane was loosening everywhere. He was kept absolutely at rest for three weeks, but his convalescence was wholly uneventful.

Careful study of the histories of these cases reveals some very instructive information. On the other hand, it serves to bring out many of the unpleasant situations that are constantly found associated with the clinical histories of diphtheria patients. Fortunately, the outcome in this series was favorable. A similar series, with almost identical histories, might have been described in which the difference of a few hours' time in the application of treatment might have been followed by fatal results. It is, to say the least, appalling that in a disease where a radical successful cure is available that the life of the child should depend on so fragile a thread as the personal equation of whether a mother is sufficiently informed to call for medical assistance whenever sore throat or hoarseness is present, and, furthermore,

whether this medical aid when called is sufficiently trained to handle the problem appropriately. There may be some remote justification in erring, if from one's errors some knowledge is gleaned. But it becomes a veritable source of horror in communicable disease hospitals to see day after day examples of the same mistakes, evidences of the same lack of comprehension and judgment to which some child's life pays forfeit. No one with even a limited experience can fail to realize the very great difficulty often associated with the clinical diagnosis of diphtheria. There are, however, certain definite diagnostic points which can be laid down and which should form a code by which every clinician should conduct himself in the management of sick children:

1. Tonsillar exudate that leaves the surface of the tonsil and spreads either to the pharynx, the uvula, or the palate should always be considered diphtheric. 2. Any exudate in the throat associated with even the mildest aphonia, hoarseness, or laryngeal cough should be immediately treated as a serious diphtheria. 3. Progressive aphonia, hoarseness, and laryngeal cough without visible exudate, particularly in children under two years of age, should be considered diphtheric. It should, furthermore, not be forgotten that in older children the laryngoscope may give valuable diagnostic information. 4. Sanguinopurulent or sanguineous discharge from one or both sides of the nose with or without visible membrane, but associated with definite evidences of toxemia, should be treated at once as diphtheria. 5. All doubtful cases should be considered true cases as far as treatment is concerned, particularly if the general signs of intoxication are pronounced.

Cultures.—In accentuating the tremendous value of accurate clinical diagnosis one must not for a moment allow the importance of culture taking to be underestimated. Particular emphasis has been laid on the clinical side of diphtheria because so many practitioners assume the attitude that they have fulfilled every obligation toward their patients if they have cultured the nose and throat, even though valuable time may be lost, time which may mean a difference of success or failure in

treatment, while they are waiting for reports from the laboratory. There is, furthermore, absolutely no excuse for the practice which is generally in vogue of waiting twenty-four hours for a bacteriologic report. Every laboratory should be equipped to make at least a tentative diagnosis in eight to twelve hours from the time the culture is submitted.

Smears.—It has been so generally recognized that smears may be negative and cultures positive that the practice of making smears has fallen into disuse. That is a lamentable error. If in 100 cases a positive diagnosis with the saving of twelve hours' time is possible in 1, the procedure is justified. Furthermore, more positive smears would be obtained if the technic of taking them were always correct. It is absurd to expect satisfactory results if one takes the swab with which he has inoculated his blood-serum to the laboratory and prepares his specimens from it. Separate swabs should be taken for this purpose and be placed immediately in a sterile test-tube. In addition, they should be examined before they become dry. It will be surprising by using a Gram stain and a differential stain how often a satisfactory result will be obtained.

Differential Diagnosis.—It is not within the scope of this discussion to enter into a full consideration of the conditions with which diphtheria may be confused, but the problem of mistaking diphtheria for peritonsillar abscess has been so strikingly brought out that it may be appropriate to call attention to certain salient facts whereby this error might have been avoided: 1, Quinsy in childhood is rare, particularly in young children. 2, Peritonsillar abscess is usually unilateral. 3, The edema and swelling develop very much more rapidly in a severe diphtheria than in peritonsillar abscess. 4, A diphtheria that simulates a quinsy is always severe and usually associated with membrane on the pharynx or palate. 5, A peritonsillar abscess either follows a follicular tonsillitis, in which case the follicular type of exudate is quite characteristic, or it starts in the deep tissues around the tonsil, in which case the tonsil is visibly pushed forward. 6, There is generally much more pain with quinsy. 7, When a diphtheric process is associated with so

much swelling and edema in the throat as to be confusing, it is accompanied, as a rule, not only by marked enlargement of the lymph-nodes, but by a great deal of periglandular edema, which is rare in peritonsillar abscess.

Antitoxin.—If the natural antitoxin content of the blood of all children of the same age were the same and if the virulence of all diphtheria bacilli were of equal degree, the administration of antitoxin might be very simple. For example, nothing would be more delightful than a situation whereby one might say that a child of given age and a given weight ill with diphtheria for a given time could be cured by the administration of an amount of antitoxin proportionate to the age, weight, and duration of the disease. Unfortunately, the question is not so simple, and whereas in a general way the size of dosage depends somewhat upon these criteria, the essential problem is always an individual one and must be handled in an individual way. There are several fundamental principles, however, that may be laid down in determining the best method of procedure: 1, diphtheria is a classical example of acute toxemia. The toxin probably exists in the affected individual in three forms, free in the blood-stream, loosely combined in the cells, completely combined in the cells. 2, It is certain that antitoxin will completely neutralize free toxin wherever it exists, and it is likewise probable that it will neutralize the toxin which is still in loose combination with the cells. It is equally certain that once the toxin becomes fixed in the cell no amount of antitoxin can ever undo the damage which has been done. 3, This conception warrants the conclusion that the ideal treatment of diphtheria depends upon the earliest possible administration of an amount of antitoxin sufficient to neutralize the toxin completely at the earliest possible moment.

With these general principles as a guide, one is forced to the following dogmatic conclusion: Always administer antitoxin in a single dose which has by previous experiences been proved sufficiently large to control a case of similar age, weight, duration, and degree of toxemia. There can be no doubt that it is better to give too much than too little antitoxin, and with

a full realization of the pathology of the disease overdosage will always insure a definite sense of security. If one gives the matter mature deliberation there can be very little question as to the advisability of single injections. When a second injection is given it means either that sufficient antitoxin was not given the first time or that the second dose was unnecessary. It is a question of neutralizing a given amount of cellular poison. Every hour that this remains potent means the death of so many more tissue cells and antitoxin in the largest amounts cannot undo this harm. The free toxin in the blood-stream is of relatively little concern. Very small quantities of antitoxin are capable of neutralizing this and of forming a barrier to any new toxin that may be formed at the site of infection. It is to make the antitoxin available to the tissue fluids and tissue cells that sufficiently large doses must be given immediately in every case. The mode of injection depends upon the judgment of the individual therapeutist. The method of choice, as far as the control of the disease is concerned, is unquestionably the intravenous route. Anyone with experience will admit this. Occasionally an untoward result will shake the confidence of even the most enthusiastic. These unfavorable results may be divided into three groups:

1, The child with status lymphaticus. These cases are, fortunately, very rare and will succumb to any unusual procedure or stimulation.

2, The child who is hypersensitive to horse-serum in the anaphylactic sense. The taking of a careful history, which should be insisted upon in every case of diphtheria, will reveal the fact that the patient has had eczema, urticaria, or asthma, is sensitive to food proteins, or has received an injection of horse-serum previously. The presence of this type of hypersensitiveness can be determined by the intracutaneous injection of 2 c.c. of a 1 : 10 solution of antitoxin in saline. If the person is sensitive there will occur at the site of injection in from a few seconds to forty minutes a characteristic wheal. These patients can be desensitized by very dilute injections of antitoxin at half-hour to hour intervals in doses of 1/1000 c.c.,

1/100 c.c., 1/10 c.c., and 1 c.c. subcutaneously, later 1 c.c. intramuscularly, and if the case is a grave one, in which intravenous therapy is to be used, 1/100 c.c. or even 1/1000 c.c. can be given intravenously, gradually increasing to the full dose. If the original reaction to the intradermal test was severe or if there was a typical history of horse-serum asthma, one might prefer to rely upon treatment by the intramuscular route.

Intravenous therapy in diphtheria has been practised so successfully in communicable disease hospitals that many authorities feel that previous desensitization is a waste of time and energy. Some experimental work by Bronfenbrenner would tend to confirm the contention that the diphtheria toxin itself in the blood-stream serves to remove any sensitiveness to horse-serum that may be present in the same individual under normal conditions. Inasmuch, however, as desensitization is so simple and takes so little time, it is preferable to carry it out before intravenous therapy is employed, and it may at times give great peace of mind.

3, The child who, for some unexplainable reason, succumbs following an intravenous injection with a group of symptoms that, for want of a better explanation, have been ascribed to some unusual colloid reaction. The mildest type of this reaction consists in a chill of variable severity followed by a sharp rise in temperature, 104° to 106° F., which comes down usually within twelve hours to normal, after which the patient is completely convalescent. In the severe types of reaction this chill becomes gradually more severe and eventually develops into a convulsive state, which may amount to practically a status epilepticus. With this, cyanosis and deathly gray pallor occur, and rapid failure of heart and respiration, associated first with delirium, and later coma, and finally death in several hours. To obviate any possibility of this dire reaction, the degree of which is unquestionably worse when larger quantities of serum are injected, it is always better after desensitizing to inject 1 c.c. of antitoxin intravenously. If this produces an unpleasant result within an hour, as evidenced by a severe chill, it will probably be advisable to give the full dose of antitoxin sub-

sequently by the intramuscular route. Unpleasant reactions of all kinds can unquestionably be very much diminished by following several very important rules: 1, Give a clear antitoxin, or, if turbid, there must be no precipitated particles present. 2, Give it slowly, $\frac{1}{4}$ c.c. per minute for the first two minutes and then 1 c.c. per minute. 3, Give the antitoxin at the temperature of the blood or a little higher, being careful not to heat the serum sufficiently high to agglutinate any protein. 4, Give a maximum dose of atropin hypodermically fifteen to thirty minutes before the intravenous injection. 5, Give adrenalin intramuscularly or intravenously in full dosage upon the appearance of any untoward symptoms after the intravenous injection.

With a full realization of these unpleasant possibilities, the fact is still paramount that successfully to treat diphtheria the antitoxin must be made available to the tissues at the earliest possible moment. It has been proved experimentally that when given by the intravenous route this availability is four times as rapid as when given intramuscularly, and ten times as rapid as when given subcutaneously. Even the most conservative must admit that whereas the intramuscular method of injection, given deeply into the gluteus muscle may be tolerable or even advisable in mild cases, the occurrence of a severe, late, neglected, or laryngeal case is an absolute and unequivocal indication for the employment of intravenous therapy. The following dosage may serve as a guide in average cases:

	Early mild cases.	Early severe and ate mild cases.	Malignant cases.
Infants under two years:			
Intravenous,	3,000 units	5,000 units	10,000 units
Intramuscular,	10,000 units	20,000 units	40,000 units
Older children:			
Intravenous,	5,000 units	10,000 units	15,000 units
Intramuscular,	20,000 units	40,000 units	60,000 units

The subcutaneous method of injecting antitoxin may be dismissed with the statement that it is only indicated to passively

immunize children who have been recently exposed to the disease. As a means of treatment it is obviously useless, pernicious, and a striking evidence of ignorance.

If antitoxin is administered in doses approximating these previously given it is conducive to at least a great sense of security. One has the assurance under these conditions that everything within the realm of human possibility has been carried out in an effort to combat the toxemia. This is particularly a source of satisfaction when one realizes that it is a frequent experience to find both the general and local symptoms of the disease increase very markedly during the first few hours after the injection of the serum. This exacerbation in the symptoms is sometimes so marked as to give the impression that the entire character of the illness has changed from what may have seemed a moderately severe or even only a mild case to one of the gravest forms. It will frequently take considerable force of character on the part of the medical advisor under such circumstances to desist from giving a second injection. If one realizes, however, that considerable time must elapse after the injection of antitoxin, even by the intravenous route before neutralization of the toxin can take place, it is not surprising that there will often be an increase in symptoms for a varying period after treatment. This is strikingly true of the local process. If the destructive action of the toxin on the superficial tissues has been severe the membrane is bound to extend to that part of the mucous membrane where the epithelial tissue is no longer visible, irrespective of how much antitoxin is given. One may, therefore, resist the temptation to give a second dose of antitoxin if he is certain from previous experience that the first injection was sufficiently large, with a full assurance that unless the administration of the antitoxin occurred too late in the course of the disease it will act as an efficient control of the toxemia.

Rest.—Aside from the specific treatment of the disease nothing is so important in the management of diphtheria as rest. Even in the mildest cases the children should be kept absolutely in bed two weeks and gotten up very gradually, allowing them to

sit up in a chair the first day one-half hour, the second day one hour, and so gradually increasing until the period reaches four to six hours, half in the morning and half in the afternoon. After this it is permissable to try some walking. In the severe cases they should be kept in bed eight to twelve weeks and only then allowed to get up when the most painstaking daily routine examination of the heart, palate, accommodation, and knee-jerks shows no evidence of abnormality.

Drugs.—With the exception of opium and its derivatives and mild laxatives there are no drugs of value in the management of diphtheria. Too much emphasis cannot be laid on the frequent and prompt use of codein or morphin hypodermically or opium in suppositories, both in those early severe cases in which mental excitement or delirium are striking features and in those cases of myocardial degeneration, both early and late, in which absolute rest is so essential. Digitalis is absolutely and unequivocally contraindicated in the treatment of this disease. Camphor and caffein seem of no value.

Local Treatment.—Three conditions call for local treatment: 1, Excessive pain in the throat. 2, Mechanical obstruction, particularly in the nose. 3, Laryngeal involvement. Where there is excessive pain incidental to the edema in the throat, great comfort may be gotten from frequently employed very hot saline irrigations. Similarly, very gently used irrigations may be of value in clearing the secretions from the nose. The employment of steam inhalations, continuous or intermittent, is advisable in all laryngeal cases. Applications of all types to the local processes are useless and definitely contraindicated.

Urinalyses.—The value of daily examinations of the urine, particularly from a prognostic standpoint, cannot be overestimated. Nothing is so valuable in determining the degree of parenchymatous degeneration. When the early albuminuria has been slight and evanescent the outlook is always good. When, however, it has been pronounced and associated with numerous casts and blood-cells, and, in spite of energetic treatment, persistent, the prognosis is always serious and less hopeful.

In conclusion it may be stated that no disease in childhood is so essentially dependent for its cure upon a clear and concise knowledge of its pathology. With this knowledge at one's disposal, however, there is no disease from the treatment of which so great a satisfaction can be obtained, when one realizes that the results represent one of the few examples in which a radical cure is directly associated with and dependent upon experimental and scientific attainment.

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THE INFLUENCE OF THE HYDROGEN-ION CONCENTRATION AND BUFFER VALUE OF FOODS ON DIGESTION, WITH SPECIAL REFERENCE TO INFANCY

IN consideration of the digestibility of foods a point which has received too little attention is the resistance which they offer to the changes in reaction essential to the activity of the various digestive enzymes. No enzyme can act except within a certain limited zone of hydrogen-ion concentration, and the specific range within which it can exert its maximum effect is more limited still. It is necessary before digestion can proceed that the food in the stomach or intestine be acidified or alkalinized to a certain fairly definite point; and it follows that the rapidity and facility of digestion will depend upon the rapidity and facility with which the reaction required by the enzymes is attained.

Resistance to change in reaction—buffer action—is a property of several major components of the common foods, particularly of the proteins and certain mineral salts, such as phosphates and carbonates. These substances are especially abundant in the characteristic food of infancy—milk. A study of the degree of buffer action in foods may, therefore, be expected to throw light on both the physiology and pathology of digestion, particularly in infancy.

The optimum reactions for the various digestive enzymes have been studied mainly *in vitro;* while the most favorable condition for their activity in the body may differ in some

respects and be complicated by other factors, there appears to be no reason to doubt that the test-tube affords an important and significant means of estimating the natural process. The chief ferments with which we are concerned may be divided into two groups, the gastric and the intestinal, the latter term including the pancreatic. To the former belong rennin,* pepsin, and gastric lipase; to the latter, the carbohydrate-splitting enzymes, lactase, maltase, invertin, amylase; the proteases, trypsin and erepsin; the pancreatic lipase. The gastric enzymes act only in an acid medium and, indeed, at two different levels of acidity, rennin and gastric lipase requiring a less acid medium than does pepsin. This fact is of great importance in an understanding of the digestion in early infancy and will be discussed later at greater length. The optimum reaction† for the curdling of milk is about P_H 5.0[3] and that of gastric lipase is at about the same point,[1, 2] the latter showing a somewhat wider range of efficiency between P_H 4.0 and 5.0. Pepsin demands a much more acid reaction. According to Davidsohn[3] its action only

* Several authorities hold that rennin and pepsin are identical ferments, exerting different effects at different levels of H-ion concentration. It is, however, convenient to keep the different terms to express the different effects. In the present article "rennin" will be understood to mean the ferment action characterized by the curdling of milk and the formation of two molecules of calcium paracaseinate from one molecule of casein.

† An explanation of the terminology of hydrogen-ion measurement will assist the reader who is unfamiliar with its technicalities. The true acidity of a solution depends upon its content of ionized hydrogen, or, as it is usually expressed, on its hydrogen-ion concentration. This depends upon the number of grams of hydrogen per liter, always a minute fraction, such as 1/1,000,000, 1/10,000,000, 1/100,000,000 gram. The greater the amount of hydrogen, the greater the acidity and the less the alkalinity, and the smaller the amount of hydrogen, the less the acidity and the greater the alkalinity. To avoid the cumbersomeness of fractions exponents of 10 were introduced and the expressions reduced to $C^H 10^{-6}$, 10^{-7}, 10^{-8}, etc. Intermediate quantities were expressed thus: 0.62×10^{-7}, which would signify 0.62/10,000,000 or 1/18,129,032 gram hydrogen per liter. The expression being still cumbersome, Sörensen suggested that the quantities be expressed by their logarithms prefixed by the sign P_H, the minus sign being omitted for convenience. Thus, 1/1,000,000 gram H, or $C^H 1 \times 10^{-6}$ becomes P_H 6.00; $C^H 0.62 \times 10^{-7}$ becomes P_H 7.258, and so on. It is important to remember that the smaller number represents the greater acidity; P_H 6.0 represents 1/1,000,000 gram H, while P_H 7.0 represents 1/10,000,000 gram H. The neutral point is P_H 7.00.

begins at P_H 4.0, while its optimum, according to Sörensen,[3] is at P_H 1.63 to 2.26, and according to Northrop,[4] at P_H 2.0 to 2.8. The slight differences found by the two investigators are probably due to slightly different experimental conditions, such as those of time and temperature; in any case an H-ion concentration less acid than P_H 3.0 would appear to be unfavorable to proteolysis by pepsin. On the other hand, a reaction less acid than P_H 4.0 is required for the curdling of milk and the splitting of fat in the stomach.

The cleavage of carbohydrates, an intestinal function, appears to be most effective at a neutral or slightly acid reaction. Pancreatic amylase, which, of the animal ferments of this type, has been the most thoroughly studied, has been found by Sherman, Thomas, and Baldwin[5] to have its optimum between P_H 6.72 and 7.09, with a zone of moderate activity between P_H 5.07 and 8.46. It is of interest to note here that Long and Fenger[6] found approximately neutral reactions in the duodenal contents of adults. Lactase has not received the thorough study which it deserves. Davidsohn,[7] working with the lactase found in the stools of breast-fed infants, noted that it was active at P_H 6.11 when tested against the whey of breast milk and at P_H 6.27 against that of cow's milk. Our knowledge of the other sugar-splitting enzymes is still more deficient. Maltase and invertin from yeast have been studied, but apparently not those from animal sources. The former, according to Michaelis and Rona,[8] has its optimum between P_H 6.1 and 6.8, while the latter, according to Sörensen,[9] has its optimum (at 18° C.) at P_H 4.4. The latter figure at least cannot be accepted as applying to human invertin. So far then as our knowledge goes, the optimum H-ion concentration for the cleavage of carbohydrates is at or near neutrality, but—if we may argue from amylase—there is a considerable range up to a marked degree of alkalinity within which they can act to some effect.

The proteolytic ferments of the intestine, trypsin and erepsin, have been found to have identical optima, both alkaline, and nearly the same range of hydrogen-ion concentration for effectiveness. Thus, Michaelis and Davidsohn[10] found trypsin inac-

tive at P_H 4.0, half active at P_H 6.7, and most active at P_H 7.7; while Rona and Arnheim[11] found erepsin inactive at P_H 4.0, half active at P_H 5.92, most active at P_H 7.7, and still q ite active at P_H 8.0. Pancreatic lipase was found by Davidsohn[12] to be most effective at a still more alkaline point. It is slightly active at P_H 6.3, fairly so at P_H 7.36, and most active at P_H 8.46. It should be mentioned that Davidsohn's experiments with lipase were conducted at a temperature of 18.5° C., and the optimum point at body temperature may possibly be somewhat different.

The normal mature digestive process, considered as based on a series of adjustments of reaction, may be envisaged somewhat as follows: In the stomach hydrochloric acid is poured out until, when the ingested food has been brought to an acidity of P_H 5.0, lipolysis begins, and, if milk has formed part of the meal, rennin action splits the casein molecule and curdling takes place by combination of the paracasein with calcium ions. As more acid is secreted, lipolysis attains its maximum rate at P_H 4.0. Still more acid brings the acidity to the point where lipolysis and rennin action diminish, but pepsin action begins, and the latter attains its full effectiveness at P_H 2.0 to 1.0.[5]

As the chyme enters the duodenum it is subjected to a gradual change toward alkalinity as its buffer action is overcome by the base poured out by the pancreas. As the P_H falls from the high gastric level to approximate neutrality, sugars, dextrins, and starch can be hydrolyzed effectively. As the chyme becomes still more alkaline—the absorption of carbonic acid assisting the change—it reaches the optimum point, P_H 7.7, for the completion of proteolysis by trypsin and erepsin, and at last that of P_H 8.5 for the completion of lipolysis by pancreatic lipase. The extreme alkalinity demanded by the last, which must be hindered to some extent by the fatty acids formed during lipolysis, doubtless has a bearing on the relative difficulty with which fats are digested.

Such is probably the mature digestive process, but in infancy, especially during the first months, the process does not appear to be fully developed. It is very doubtful whether much before

the age of one year there is a sufficient degree of acidity in the infant's stomach to permit a marked degree of digestion by pepsin and whether in the first month or two of life even this occurs to a significant extent. Kronenberg's[13] illuminating study showed that only rarely is the gastric acidity greater than P_H 4.0 under the age of fourteen months, while the average was but P_H 5.0. The highest value he was able to find under one year was P_H 3.0 in an eight-month infant fed on cow's milk, while the maximum for a breast-fed infant was P_H 3.45. The highest value in his series was P_H 2.5 at eighteen months, which he states to be the *average* for adults.*

The secretion of acid in the stomach of young infants would therefore appear to be normally less abundant and to cease at a point of lower H-ion concentration than in after life. The burden of digestion, in consequence, is at this age thrown mainly on the intestine; indeed, during the first weeks of life it may be almost wholly there. The pyloric sphincter at this time seems to relax very readily and to allow a large proportion of the freshly ingested meal to pass into the duodenum before the gastric secretions can have had more than the slightest effect upon it. The fact is well known to pediatrists that infants commonly ingest at one feeding a volume two or three times as great as the anatomic capacity of the stomach; indeed, examined under the fluoroscope, food can be seen spurting from the stomach while the infant is still feeding. Under normal conditions pyloric control and gastric digestion probably develop gradually, and *pari passu*, as the oxyntic glands increase their powers of establishing higher and higher levels of acidity and thus of affording optimum conditions for the peculiar gastric enzymes. We may conceive that during the earliest period little or no gastric digestion occurs; then curdling and gastric lipolysis appear; finally, after a considerable interval, a level of acidity is reached which permits pepsin to act. Until this time the burden of proteolysis must be carried by the intestine.

* At the time this article is prepared Marriott's paper, read at the 1922 meeting of the American Pediatric Society, is available only in abstract. He appears to have found somewhat higher acidities than Kronenberg, but not, however, approaching the optimum for pepsin.

The considerations presented point clearly to the importance of the initial acidity and the buffer properties of foods in affecting their digestibility. In unbuffered solutions, to be sure, the initial reaction is of minor importance because in them minimal quantities of acid or base suffice to produce maximal changes in reaction, but a considerable quantity of buffers is, in fact, usually present, at least in the foods of infancy. The degree of change from the initial reaction to the desired reaction for enzymic efficiency will be attained with ease or difficulty, with a small or large amount of acid or basic secretion, according to the amount of buffers present. Present in moderate amounts these substances may well act as the normal stimulus to gastric and pancreatic secretion of acid or base. Absent or present in too small amounts they may fail to provide the normal stimulus and so delay the development of normal digestive function. Present in excessive degree they may prevent digestion or lead to premature and excessive activity of the secretory glands.

Aron[14] has studied the acid-combining power of human and cow's milk, but not its base-combining power. His curves show that human milk has a much smaller acid-combining power than has cow's milk. Allemann[15] also noted the high buffer content of cow's milk, which he ascribes to the large amount of secondary phosphates present.

In the experiments here reported an effort was made to determine the initial reaction and the degree of buffer resistance both to acid and alkali in a number of foods such as are ordinarily fed to young infants. The electrometric method of hydrogen-ion estimation was used throughout. The calorimetric method with the turbid solutions and suspensions under examination presented too many technical difficulties to be of value. For the electrometric estimations the set-up designed by Dr. Carl Schmidt, of the University of California Medical School, with readings made on a voltmeter and translated into values of P_H with the help of his tables, was employed and found satisfactory. The accuracy of the readings was checked from time against standard buffer solutions prepared according to Clark. As a rule, 20 c.c. quantities of the test solutions were used, but for

convenience the results have been entered in the tabulations here given in values for 100 c.c.

In general, three means of approach to the problem were adopted. First, the initial reaction of each food was determined. Second, the curve of reaction change was followed as the solution or suspension was titrated with tenth-normal NaOH and HCl. Third, the amounts of tenth-normal HCl and NaOH required to bring the material to hydrogen-ion concentrations of P_H 5.0 and P_H 7.7 respectively were found. These points were selected for their bearing on ferment action; P_H 5.0 on the acid side because it is the point at which rennin and gastric lipase, and P_H 7.7 because it is the point at which trypsin and erepsin act with maximum efficiency. It is regretted that the present report cannot include titrations to P_H 2.0, the approximate optimum for pepsin, a study which we hope to complete for later publication. Since during the normal course of digestion in the body foods are first acidified and then alkalinized a few experiments analogous to this were also made, bringing the material first to an acid point and then in the same sample to an alkaline, with a view to determining the effect on the buffers.

The results of our experiments are summarized in the following tables:

TABLE I

PRIMARY ACIDITIES

	P_H
Colostrum:	
Sample 1	7.71
Sample 2	7.20
Sample 3	7.96
Sample 4	7.84
Sample 5	8.01
Average	7.74
Cow's milk (50 samples):	
Lowest	6.58
Highest	7.08
Average	6.89
Diluted milk:	
1 part milk (P_H 6.89), 2 parts distilled water	7.09
2 parts milk (P_H 6.80), 1 part distilled water	6.96
Whey (P_H of original milk, 6.97)	7.00

Lactic acid milks:

Fer-mil-lac 4.55
B. Acidophilus milk:
Twelve hours' incubation 6.48
Eighteen hours' incubation 6.02
Twenty-four hours' incubation 5.52
Protein milk (made with fer-mil-lac) 5.35

Carbohydrate foods:

One per cent. barley-water:
Robinson's, in distilled water (P_H 6.98) 5.93
Robinson's, in tap-water (P_H 7.7) 7.84
Mead's, in distilled water (P_H 7.0) 6.14
Mead's, in tap-water (P_H 7.7) 8.30
Mead's Dextrimaltose No. 1, 5 per cent., in distilled water 7.10
Mead's Dextrimaltose No. 3, 5 per cent., in distilled water 8.03
Mellin's Food, 5 per cent., in distilled water 7.72
Borcherdt's Malt Soup, 5 per cent., in distilled water 7.15
Loeflund's Malt Soup, 5 per cent., in distilled water 6.17
Eskay's Food, 5 per cent., in distilled water 7.47
Karo Corn Syrup, Blue Label, 10 per cent., in distilled water 6.20
Karo Corn Syrup, Red Label, 10 per cent., in distilled water 5.75

Milk mixtures:

Mellin's Food, 5 per cent., in whole milk (P_H 6.90) 7.20
Dextrimaltose No. 1, 5 per cent., in whole milk (P_H 6.89) 6.86
Dextrimaltose No. 3, 5 per cent., in whole milk (P_H 6.95) 7.25
Borcherdt's Malt Soup, 5 per cent., in whole milk (P_H 6.91) 6.83
Loeflund's Malt Soup, 5 per cent., in whole milk (P_H 6.91) 6.98
House formula No. 1 (whole milk, 400; Red Label Karo, 120; 1 per cent. barley-water, 480) 6.88
Lime-water (U. S. P.) 12.56

TABLE II

SHOWING AMOUNTS OF N/10 HCl AND N/10 NaOH REQUIRED TO BRING 100 C.C. TO P_H 5.0 AND P_H 7.7 RESPECTIVELY

	Initial P_H.	HCl, c.c.	NaOH, c.c.
Colostrum:			
Sample 1, yellow	7.71	15.0	0
Sample 2, white	7.20	17.5	0.40
Cow's milk:			
Whole	6.91	45.0	11.0
Diluted, two-thirds milk	6.90	30.0	7.0
Diluted, one-third milk	7.07	15.0	2.0
Whey	7.00	18.0	8.0

Lactic acid milks:			
B. Acidophilus milk:			
Twelve hours' incubation	6.48	39.0	18.5
Eighteen hours' incubation	6.02	30.0	33.0
Twenty-four hours' incubation	5.52	14.5	50.5
Protein milk (made with fer-mil-lac)	5.53	5.0	75+
Supernatant fluid from protein milk	5.39	5.0	46.5
Carbohydrate foods:			
One per cent. barley-water:			
Robinson's, in distilled water	5.79	0.3	0.7
Mead's, in distilled water	6.14	0.5	0.6
Robinson's, in tap-water	7.84	3.3	(0.2)*
Mead's, in tap-water	8.30	3.6	(0.5)
Mead's Dextrimaltose, No. 1, 5 per cent., in distilled water	7.10	1.1	3.5
Mead's Dextrimaltose, No. 3, 5 per cent., in distilled water	8.03	13.1	(2.5)
Mellin's Food, 5 per cent., in distilled water	7.72	15.0	(0.4)
Borcherdt's Malt Soup, 5 per cent., in distilled water	7.15	6.0	2.5
Loeflund's Malt Soup, 5 per cent., in distilled water	6.17	2.0	3.4
Eskay's Food, 5 per cent., in distilled water	7.47	2.0	0.5
Karo Syrup, Blue Label, 10 per cent., in distilled water	6.20	0.6	0.2
Karo Syrup, Red Label, 10 per cent., in distilled water	5.57	0.2	0.4
Milk mixtures:			
Mellin's Food, 5 per cent., in whole milk	7.20	60.0	11.5
Dextrimaltose No. 1, 5 per cent., in whole milk	6.86	47.5	12.5
Dextrimaltose No. 3, 5 per cent., in whole milk	7.25	60.0	7.5
Borcherdt's Malt Soup, 5 per cent., in whole milk	6.83	50.6	10.5
Loeflund's Malt Soup, 5 per cent., in whole milk	6.98	50.5	14.5
House formula No. 1	6.88	22.5	10.0
Lime-water (U. S. P.)	12.56	49.7	(45.0)

Effect of Dilution.—Reference to the figures for whole and diluted cow's milk and for colostrum show that the last has only about one-third the acid-combining power of whole cow's milk and in consequence that it is necessary to dilute cow's milk with 2 parts of water to provide a mixture having the same buffer value (on the acid side) as that of the infant's natural food. The need of dilution for cow's milk formulas is clearly brought out

* Figures in parentheses signify that acid instead of alkali was used to bring the material to P_H 7.7.

by these facts, as well as the approximate degree. The digestive apparatus of young infants fortunately has a considerable adaptive power, so that high dilution is not necessary for long periods. It is, however, important to remember why dilution is necessary at the outset of bottle feeding and to make changes from high to low dilutions gradually. It may be worth pointing out, also, that the acid and base-combining power of diluted solutions is directly proportional to the dilution.

Effect of Successive Additions of Acid and Base to the Same Sample.—It might be supposed that in order to neutralize a given quantity of acid that had been added to milk it is necessary merely to add an equal quantity of alkali of equivalent strength. Arguing from such a premise, if 100 c.c. of milk had been acidified to P_H 5.0 by the addition of 4.5 c.c. of normal HCl, and we wished to restore the original reaction, it should be necessary to add just 4.5 c.c. of normal NaOH. This point has a practical bearing on digestion, since the intestine has to neutralize the acid secreted by the stomach before it can produce the necessary reaction for its own ferments, and the quantity of base required for it to do this is a matter of importance. If some of the gastric acid is "bound" by the occurrence of an irreversible reaction in the stomach, less base would be required to neutralize. The protocols of the following experiments indicate that this is the case.

Experiment 1: Whole cow's milk, P_H 7.06, 20 c.c. quantities.

10 c.c. N/10 HCl added. Stood five minutes. P_H 4.97.
Stood five minutes.
10 c.c. N/10 NaOH added. Stood five minutes. P_H 8.10.

Experiment 2: Whole cow's milk, P_H 7.06. 20 c.c. quantities.

A. 1 c.c. N/10 HCl added. Stood five minutes. P_H 6.97.
1 c.c. N/10 NaOH added. Stood five minutes. P_H 8.10.
B. 1 c.c. NaOH added. Stood five minutes. P_H 8.14.
C. 1 c.c. HCl added and immediately afterward 1 c.c. NaOH. P_H 7.10.
D. 1 c.c. NaOH added and immediately afterward 1 c.c. HCl. P_H 7.06.

Experiment 3: Colostrum, P_H 7.84. 10 c.c. quantities.

A. 1.5 c.c. N/10 HCl added. Stood five minutes. P_H 5.42.
1.5 c.c. N/10 NaOH added. Stood five minutes. P_H 7.98.

Experiment 4: Colostrum. P_H 7.96. 10 c.c. quantities. 1.5 c.c. HCl added. Stood five minutes. P_H 5.46. 1.5 c.c. NaOH added. Stood five minutes. P_H 8.46.

It is interesting to note that when acid and base are added to milk in rapid succession the original reaction of the milk is obtained, but that when the acid has been allowed to remain five minutes in the milk the addition of the equivalent amount of base brings the reaction to a considerably more alkaline point than the original. The accuracy of the observation was checked by two duplicate experiments. These observations point to the fact that a certain amount of the gastric acid is bound in some irreversible combination, lightening considerably the task of basic secretion in the intestine, a process which appears to hold for human as well as for cow's milk. It may be mentioned here that the physical condition of both milks is more favorable to intestinal than to gastric digestion. Thus, whole cow's milk requires four times as much acid to bring it to the initial optimum for gastric digestion as base to bring it to the intestinal optimum, while colostrum at least is already at the latter point.

Colostrum.—The present experiments with colostrum, defined as the mammary secretion of the first two weeks of lactation, are, so far as we know, the first of their kind, and their bearing on the physiology of digestion in early infancy may be considered.

It is a well-recognized fact that during the first period of postuterine life the milk ingested by infants in large part leaves the stomach very soon after ingestion, probably before it can have been subjected to any significant extent to the action of the gastric secretions. It is, therefore, interesting to find that the average reaction of five samples of colostrum was P_H 7.74, or almost exactly the optimum for trypsin and erepsin and nearly that for pancreatic lipase. For the digestion of protein and fat, therefore, there would be practically no demand for base, provided the food were placed directly in the intestine. For the action of rennin and gastric lipase, on the other hand, a large amount of hydrochloric acid would be necessary, equivalent to 15 c.c. of tenth-normal acid for each 100 c.c. of colostrum (see

Table II). With our limited knowledge of the conditions favorable to the action of lactase we cannot say definitely how well they are met by the conditions actually present. The reaction of colostrum would, however, appear to be somewhat alkaline for the maximum degree of saccharolysis. Difficulties in the digestion of this sugar are familiar to pediatrists. The occasional appearance of lactose in the stools, the frequent occurrence of colic in young breast-fed infants, and the normally acid reaction of the stools (due to fermentation?) have all been ascribed by clinicians to the difficulty of lactose digestion.

One may conceive that the normal process of digestion of breast milk in the young, healthy infant is about as follows: The first part of the meal passes through the stomach without change into the intestine, with its reaction favorable to proteolysis and lipolysis, but partly inhibitory to the cleavage of lactose. The latter portion of the meal, retained in the stomach for a period of time, becomes acidified enough for curdling, separation of the whey, some lipolysis, and perhaps (after the age of a few weeks or months) some degree of proteolysis by pepsin; passing into the intestine it is first neutralized, permitting lactase to act, and then alkalinized for the completion of proteolysis and lipolysis. During the first weeks of life the gastric quota of digestion is relatively slight, gradually increasing in importance with increasing age, and perhaps not reaching the proportions of maturity earlier than the third year.

Cow's Milk.—Fresh, bottled, unpasteurized cow's milk obtained for this laboratory has shown a fairly constant hydrogen-ion concentration. Of 50 specimens examined, the most acid showed a P_H of 6.57, and the least acid, a P_H of 7.08, the average of the series being 6.89. The initial reaction of cow's milk is of importance because of the high content of buffers which are present, resisting changes in reaction. Thus, 45 c.c. of tenth-normal HCl are required to bring 100 c.c. of milk to the gastric optimum of P_H 5.0, and 11 c.c. of tenth-normal NaOH to bring it to the intestinal optimum of P_H 7.7. The force of Clark's[16] objections to the use of lime-water, sodium citrate, and milk of magnesia, all of which give the stomach a still greater task of

acid secretion, is evident. Such basic substances in milk undoubtedly do prevent the curdling of milk because they prevent the attainment of a reaction which would permit any gastric digestion to occur. The feeding of milk formulas containing them would appear to throw the entire burden of digestion on the intestine, a function which doubtless it can usually maintain. Long continued, such feeding might conceivably seriously delay the development of gastric function, or in some instances lead the stomach into disorders of hypersecretion as the result of an effort to establish its function against odds.

Whey, with its initial reaction at neutrality (P_H 7.0), an acid resistance about two-fifths, and an alkaline resistance about one-seventh that of whole milk, presents conditions of hydrogen-ion on concentration and buffer effect not so very different from those of breast milk.

Lactic Acid Milks, Including Protein Milk.—This group of foods is characterized not only by a high initial acidity, ranging from P_H 4.55 to P_H 5.52, but also by a high degree of resistance to alkaline change. The latter is particularly marked in the case of protein milk, in which there is present not only the acid products of lactic acid fermentation, but also a large amount of casein buffer. To bring a given volume of protein milk to P_H 7.7 it is necessary to add more than three-quarters as much of tenth-normal NaOH.

It is one of the most puzzling questions in pediatrics why a food thus constituted should be the most valuable of therapeutic agents in the treatment of various intestinal disorders. It is almost specific in its effect upon a group of the most severe diarrheas of infancy, causing a cessation of the frequent, watery, highly acid stools and the evidences of acidosis, and causing the appearance of firm, pasty stools having a definitely alkaline reaction. Protein milk has been used also with striking benefit in marasmus (here lactic acid milk with corn syrup has also been used with strikingly good results, as Marriott has shown), in chronic intestinal indigestion, and other conditions equally dissimilar from the acute diarrheas. Intolerance to sugar and the benefit arising from the use of a food low in that element—

Finkelstein's original explanation—is no longer accepted as an adequate explanation, for considerable quantities of sugar, particularly of the dextrin-maltose combinations, can be added to protein milk without depriving it of its characteristic effect.

Arguing from its initial reaction and its buffer action, another hypothesis may be suggested. Protein milk has a reaction which allows it to be attacked directly by gastric lipase and with some further addition of acid—probably not much, since its acid-absorbing powers have largely been exhausted—by pepsin. May it not be that a food such as this allows the stomach to take over a greater share of the digestive function which the intestine, embarrassed in the presence of excessive or pathologic bacterial activity, or perhaps in the case of marasmus and coliac disease by impaired function of the pancreas, cannot carry alone? By thus increasing its activity, splitting a greater proportion of the fat, and giving the casein a more thorough preliminary proteolysis, the stomach could greatly facilitate such digestive function as can be performed only by the intestine. It has been recognized since protein milk was introduced that it fails to exert its beneficial effects in very early infancy. There are certain indications, already discussed, that at this age the gastric functions are largely undeveloped, and it may well be that they cannot be stimulated quickly or assisted to the point where they can take over digestion sufficiently for the process just outlined. It has also been frequently noted that a satisfactory gain in weight is hard to obtain on protein milk feeding. It seems possible that this may be due in part at least to the combination of calcium and the fatty acids, leaving less of the latter to form in and irritate the intestine but withdrawing in insoluble form a considerable portion of the calories of the food. It is an interesting question whether the calcium soaps are a characteristic product of gastric lipolysis, formed at a point where calcium salts and the split products of fat are most intimately in contact.

Carbohydrate Foods.—*Barley Flour.*—Barley-water, made from either Robinson's or Mead's barley flour, shows only an insignificant buffer action. In contrast with lime-water, used

for the same purpose of altering curd formation, it interferes no more with the changes in reaction vital to digestion than the distilled or tap-water used in their preparation.

Hydrolyzed Starch Foods.—To this group belong those foods made from starch or whole grain under the action of hydrolyzing agents. Most of them are prepared with diastatic ferment, such as malt, but some (probably including corn syrup) are hydrolyzed by acid. Some of them contain a considerable proportion of protein and mineral salts from the whole grain, but most of them, being made from a more or less purified starch, contain only minimal quantities of such ingredients. Finally, to some of them potassium carbonate has been added.

None of these foods has any marked buffer value. Mellin's Food and Mead's Dextrimaltose No. 3, both containing potassium carbonate, are rather alkaline; Eskay's Food is somewhat less so; the others, such as the malt soups, Dextrimaltose No. 1, and the corn syrups, are either neutral or slightly acid. Mellin's Food and Dextrimaltose No. 3 require a considerable proportion of acid to reach the gastric optimum and so may be assumed to be more suitable for intestinal digestion than for gastric, but the rest show so little resistance to reaction change that they can affect the digestibility of the formulas to which they are added to only an insignificant extent. The corn syrups have practically no buffer action.

A few examinations were made of mixtures of milk and the carbohydrate foods, with results shown in Table II. They require no more comment than that the total buffer action of the mixture is equal to the sum of its components.

Lime-water.—We can merely corroborate Clark's observations, already quoted, showing the striking effect of lime-water on alkalinity. So alkaline is this solution that it is necessary to add acid in large amounts to bring it to the intestinal optimum alkalinity. Formulas to which it has been added would present great difficulties to gastric digestion.

CONCLUSIONS

1. The bearing of the initial hydrogen-ion concentration of foods and their content of buffer substances on the efficiency of digestion, especially in infancy, has been discussed. Optimum conditions for the action of the various digestive enzymes demands that certain grades of acidity be established in the stomach and of alkalinity in the intestine. The ease of digestion of a given food will depend on the ease with which it permits the requisite reactions to be established in the gastro-intestinal tract. Tables showing the initial reaction and the amounts of acid and alkali required to produce two typical optimum reactions have been given.

2. The reaction and buffer properties of colostrum indicate that it is intended for intestinal digestion rather than for gastric. The development of gastric digestion is believed to be a gradual one, probably not completed for a considerable period under normal conditions.

3. The reaction and buffer properties of protein milk and lactic acid milks suggest that their curative effect may be due to a stimulation of gastric function to take up a greater share of digestion.

4. Most of the carbohydrate infant foods have little or no buffer value and hence do not materially affect the digestibility of milk. Those foods, however, to which potassium carbonate has been added are somewhat alkaline and interfere to some extent with gastric digestion.

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INTESTINAL PROTOZOA

AMEBIC DYSENTERY—SEVERE ULCERATIVE COLITIS—GIARDIA—CHILOMASTRIX

RECENT advances in the study of protozoan infections of the intestine have added greatly to the ease and accuracy of their diagnosis. The gain has been chiefly in the recognition of the cyst forms from which an absolute diagnosis can be made even in the absence of the active parasite. An intelligent routine examination of the stool soon reveals that the source of the symptoms in a small but definite percentage of the patients seen in temperate climates is a protozoan parasite. More important, the great majority of these are chronic and carrier cases in whom the symptoms are entirely different from the better-known acute cases, and in these the cyst form of the parasite is often the only evidence of the infectious agent. A better knowledge of the morphology, appearance unstained and stained, and differential diagnosis between pathogenic and non-pathogenic varieties is clarifying not only the diagnosis but also the problem of treatment. The disease was encountered thirty-six times in 700 cases of all sorts in which the stool examination was personally made during the past year, a percentage of 5.1. Chronic, quiescent, and carrier cases are much more frequent than acute cases. These do not have the bloody diarrhea, in fact, may be markedly constipated. Chronic ill health, sallow color, and tenderness over the colon are likely to be the chief symptoms. Diagnosis depends upon detection of the cyst forms of Entamœba dysenteriæ (histolytica) in the stool. Because most clincians are not

familiar with the technic of stool examination, these cases are often overlooked completely. Since they produce the cysts which are the sole means of infecting others with dysentery, and since they are subject to acute exacerbations of the disease or the complications, such as liver abscess, it is important to know the technic required for their diagnosis.

Case I.—Amebic Carrier Relapsing Into Acute Dysentery After Operative Procedure.—The first case is presented because it illustrates the problem of amebic dysentery as seen in temperate climates. I am indebted to Dr. W. J. Kerr for permission to report this case from his private series. It is unusual in that the cause of the relapse into acute bloody dysentery was an operative procedure. The patient, P. B., thirty-six years of age, had spent much of his childhood in Siam. He entered the Hospital November 8, 1921 (U. C. Hospital No. 12,906), complaining of attacks of epigastric and right upper quadrant pain, nausea, vomiting, sense of pressure and distention in the epigastrium, and belching. The duration was ten years, with an average of four or five attacks yearly. He was chronically constipated. The urine, blood, blood Wassermann, and spinal fluid were normal. There was distinct radiographic evidence of duodenal ulcer with possible involvement of the gall-bladder. A barium enema was made to pass to the cecum with some difficulty because of spasm, yet no defects, narrowing, or localized tenderness could be found. The stool on three examinations (November 12th, 14th, and 21st) contained typical cysts of Entamœba dysenteriæ (histolytica). The smears stained with iron hematoxylin which you see under the microscopes were made from these specimens. You will note that the cysts contain from one to four nuclei, and never more. The nuclei have the typical central dot and peripheral ring of chromatin which is characteristic of E. dysenteriæ. Also you will note that some of the cysts contain a single large bar of chromatoidal substance with rounded ends, while others have multiple small bars. All of the cysts are of medium size, as compared with the large eight-nuclear cysts of the non-pathogenic E. coli and the very

small cysts of the non-pathogenic E. nana, both of which are common in stools. The maximum of four nuclei and the chromatoidal bars with rounded ends differentiate cysts of E. dysenteriæ from those of E. coli. The difference in the nuclei alone is sufficient for differentiation from E. nana. Absolute diagnosis can be made from these stained smears and with only the cyst forms present. The technic of staining with iron hematoxylin is not particularly difficult, and the preparation can be put through the stains and mounted for inspection in fourteen minutes, using the rapid method of Kofoid and Swesy.

Little being known of the possible effects of operation on chronic dysenterics, no emphasis was laid on the stool findings and the patient was sent to surgery on November 21st. Ulcers, two healed and one active, were found in the duodenum, as well as dense adhesions between the liver and diaphragm. Also the gall-bladder showed marked evidence of chronic inflammation, there being many fiddle-string adhesions reaching to it from one of the ulcers. No definite proof was found that the disease in the right upper quadrant was due to the amebic infection. Posterior gastro-enterostomy, cholecystectomy, and appendectomy were done.

Immediately following the operation the patient began to have loose movements which increased in number daily. Little attention was paid at first because a bronchial infection was the chief source of concern. The movements were merely soft and mucoid in the beginning, but by the fifth postoperative day he was having nine movements in twenty-four hours and they had begun to be bloody. By the seventh postoperative day the distress and pain from the diarrhea had become the dominant feature of the convalescence. A stool specimen sent to the laboratory on this day (November 28th) was liquid, the color of old blood, small in amount, and consisted almost entirely of pus, blood, and mucus, with large numbers of active amebæ. I have placed the smears from this specimen stained with iron hematoxylin under the microscopes. You will note the typical active form of Entamœba dysenteriæ (histolytica). One of the amebæ contains eight red blood-corpuscles, in which the hemoglobin is

still evident in spite of the stain. The nucleus has the typical central dot and peripheral ring of chromatin. The remainder of the smear consists of disintegrating pus-cells, red blood-corpuscles, and mucus with bacteria enmeshed in it. No food residues are evident. Treatment with emetin hydrochlorid subcutaneously was started, with opium to quiet the diarrhea, pain, and tenesmus. In spite of this he continued in an extremely critical condition for four days, the number of stools reaching a maximum of twelve in one day. From the eleventh postoperative day to the twenty-second gradual but definite improvement took place, the diarrhea was brought under control, the character of the stools changed, and all the symptoms abated. On December 20th, the twenty-ninth day after operation, the stool was formed and normal appearing in every way. Microscopically there were no amebæ, cysts, blood, pus, or mucus. A similar normal condition was found on stool examination on January 5, 1922. A great gain in strength and weight having occurred, the patient left the hospital on January 9th to continue his convalescence in the country. Today, July 28, 1922, he reports himself quite well and free from symptoms.

The term "cure" is very loosely used in regard to amebic dysentery. Treatment of acute cases, even with emetin, usually drives them merely into the quiescent or carrier stage, in which the patient may regain a condition of fair or even good health, but the stool will show amebic cysts. These cysts always mean ulcers with active amebæ somewhere in the colon. As soon as the condition warrants after the acute attack, intensive treatment with emetin by mouth, subcutaneously, and even with a few salvarsans thrown in, should be tried in order to get a complete cure. Some such standard of cure as that of Dr. C. A. Kofoid should be adopted generally. The stool is examined on three successive days three months after treatment, on six successive days at six months, and on ten or more successive days at one year. If all are negative, a cure is claimed. Eradication of the parasite does not insure relief of the symptoms, particularly in long-standing cases. Scar tissue remains in the colon and, if extensive, may interfere permanently with its

function. This phase of the subject is well illustrated by our next case. The problems in Balantidium coli and Craigia infections are essentially the same as in amebic dysentery.

Case II. Severe Ulcerative Colitis—Relief by Surgery.—E. L., U. C. Hosp. No. 1105, twenty-three years old, single, white, had lived most of his life in the San Joaquin Valley, and had a negative family and past history. At sixteen years of age he developed a diarrhea. There were only three or four loose, not watery, movements a day at the time of onset. Occasionally he had a colicky pain in the left lower quadrant, always relieved by defecation. Later, mucus and an occasional small amount of blood were noted. Because of these symptoms he was placed in a sanitarium at Modesto for two weeks and given 60 grains of ipecac by mouth, followed by hypodermic emetin. No benefit resulted, in fact, he became worse.

On February 4, 1916 he entered the U. C. Hospital for the first time. He was then having ten or twelve bowel movements a day, with only occasional small amounts of fresh blood. General examination was negative. Proctoscopic examination showed a relaxed anal sphincter, intensely hyperemic and edematous mucosa, covered by a grayish membrane which peeled off easily, leaving bleeding points, and definite ulcerations of the sigmoid. Blood Wassermann, von Pirquet, urine, blood, and stomach contents were negative. A course of emetin hydrochlorid (subcutaneously) was given, together with smooth diet, irrigations, suppositories of opium and atropin, and so forth. There were short periods of improvement during the month and a half of medical treatment, but it was felt that no permanent headway was being made. No amebæ or dysentery bacilli were ever found in the stools. Temperature, pulse, and respiration were always within physiologic limits. Since the stools continued to be as frequent as fifteen to twenty a day and were accompanied by severe gripping pain, it was decided to return the patient to surgery for exploratory laparotomy and colostomy to rest the inflamed lower bowel. Operation by Dr. W. I. Terry on March 22, 1916 disclosed marked injection of the large intestine and

first 2 feet of the ileum. A "subacute" appendix was removed. No other pathology was found except hypertrophied lymph-glands. Colostomy was done. The postoperative course was not severe, symptoms decreased, the patient felt much better, and was discharged April 21, 1916. Seen in 1917 and 1918 the patient had regained his normal weight and was living very comfortably.

August 27, 1919 the patient returned to the Surgical Service requesting closure of the colostomy opening over which he had no control, while nothing was being passed by rectum. He had been feeling well, was not disabled, and was at his normal weight, but naturally wanted his intestinal contents to pass by the usual route. Again his general examination was negative. A Widal and blood-culture taken during an attack of influenza had been negative. Dr. H. C. Moffitt, in consultation, wrote the following note: The rectal mucosa, while showing no ulcerative condition now, is more injected than usually seen and the bowel itself is more spastic than normal. An operation to restore the normal circulation of intestinal contents would be more or less experimental in nature, but if the patient wishes to run the chance of a possible second colostomy operation, it would seem advisable to wait no longer before going ahead with such treatment. At the patient's request, after explaining the situation to him, Dr. W. I. Terry on August 29, 1919 closed the colostomy and performed an ileocolostomy. The postoperative course was rather severe, with vomiting and abdominal pain. On the twelfth day a fecal fistula was established, and later two more below the first. He continued to have attacks of severe epigastric pain, but gradually, as the fistulæ took care of the fecal stream, regained appetite, strength, and spirits. He was discharged October 28, 1919, feeling well, but with the abdominal fistulous openings which at times discharged a purulent material and at times fecal matter.

February 18, 1920 the patient returned to the Surgical Service to have the abdominal fistulæ closed. Since leaving the hospital four months before he had been feeling very well, but the fistulæ had been discharging a small amount of purulent

matter. He had been passing soft stools by rectum until three days before entry, when the fistulous discharge became quite profuse. General examination was again negative. Three fistulæ were found in the abdominal scar. At operation, March 3, 1920, Dr. J. H. Woolsey found several loops of bowel bound by dense scar tissue to the peritoneal side of the scar. These, with the fistulæ, were resected. The patient was sent to the ward in poor condition and spent several stormy days thereafter. Four days after operation there was fecal vomiting and great pain. Dr. Woolsey again operated for intestinal obstruction, and a loop of ileum was anastomosed to the transverse colon with a Murply button. There followed another stormy session and soon a fecal fistula was present again in the first scar. The second healed well. In this condition he was discharged on May 5, 1920 feeling very well.

September 22, 1920 he re-entered the hospital because of recurrence of his original colitis. The operation the previous March had returned the fecal stream successfully to its normal channel, the remaining fistula finally discharging merely a small amount of seropurulent material. The bowel had not functioned normally at any time, there being three or four soft movements per rectum daily. Two weeks before entry diarrhea started, and within three days he was having twenty-four movements a day, with associated severe crampy pains in the left lower quadrant, which radiated downward into the groin. A bowel movement always relieved the pain. Small amounts of blood were occasionally passed, the stools always being very soft, mucoid, dark colored, and small in amount. There had been no fever, chills, or vomiting. One week before entry the abdominal fistula began to discharge large amounts of fecal material, with a resulting decrease in the movements per rectum. Physical examination was again negative except for the fistula in the right rectus scar. Hemoglobin was 78 per cent., red cells 4,224,000, white cells 18,500. The smear showed neutrophils 68 per cent., lymphocytes 28 per cent., large mononuclears 3 per cent., and transitionals 1 per cent. The urine was normal and the blood Wassermann again negative, with two antigens.

Proctoscopic examination revealed a much thickened bowel wall with narrow lumen. The mucosa was generally granular, bled easily, and was covered with a grayish film in the upper rectum. No definite ulceration was visible. The proctoscope could not be inserted into the sigmoid. The stools microscopically showed much mucus, pus, and a little blood. A fresh specimen on two occasions was diagnosed by an able zoölogist as containing large numbers of active Entamæba dysenteriæ (histolytica). The smear stained at the time with iron-hematoxylin is presented for your inspection. In it will be seen very many endothelial cells in various stages of degeneration. No absolutely definite amebæ can be found. These endothelial cells occur normally in all exudates and are often present in enormous numbers in the stools of colitis cases. Wenyon and O'Connor find them in the greatest numbers in bacillary dysentery, but they will be found in all exudates from the colon. They lack the nucleus of Entamæba dysenteriæ (histolytica) and their inclusions stain black and vary greatly in size. In the unstained fresh smear they look exceedingly like small amebæ, but never show any but the most sluggish ameboid motion, certainly nothing resembling the quick protrusion of clear pseudopodia so characteristic of Entamæba dysenteriæ. These cells often contain "fatty" inclusions that closely resemble red blood-corpuscles, but in the stained smears these are seen to contain no hemoglobin.

Cultures from the rectum showed Bacillus coli and Streptococcus hemolyticus beta; from the stool, Morgan's bacillus, fairly numerous, but negative for other organisms of the typhoid-dysentery group; from the fecal fistula, Morgan's bacillus. No acid-fast bacilli could be demonstrated. Screen and *x*-ray plates showed a very contracted colon. The enema entered the small intestine immediately after reaching the hepatic flexure.

During the four months from October 22, 1920 to February 22, 1921 the patient was kept in the hospital on medical treatment without benefit. In order, he had tincture of opii, bismuth, colonic irrigations with 1 : 10,000 silver nitrate, calcium chlorid

5 per cent. solution intravenously, 10 per cent. glucose intravenously, opium suppositories, belladonna, emetin hydrochlorid subcutaneously plus emetin-bismuth-iodid by mouth, and neosalvarsan intravenously. At the conclusion he was emaciated, having as many as twenty-five bowel movements a day, and constantly losing ground.

On February 17, 1921 Dr. J. H. Woolsey made the following note: The course of this condition shows that a short time following the return of the fecal current to the colonic area the old colitis returned; that it does not improve as long as it is irritated by the fecal stream, and suggests strongly that a diverting of this fecal stream completely would allow healing as it did before.

On February 22d permanent ileostomy was done. The cecum and ascending colon were found to be atrophied to one-half the normal length and caliber. The remaining colon and sigmoid showed decrease in size also, but with great thickening of the wall, absence of haustræ, and approximation of longitudinal bands. Multiple adhesions bound the many coils of the small intestine. There was less postoperative distress than after the previous operations, and he soon gained in weight and strength, improved in color, and lost all the symptoms of colitis. Thus he finally returned to the same point where he was after the first operation, the only difference being that he was at last convinced that he must retain his colostomy or ileostomy indefinitely in order to remain comfortable. By the use of Lassar's paste and plenty of cotton he is able to avoid many of the disagreeable features of a permanent ileostomy. As you see him today (July 28, 1922) there is nothing to differentiate him from any other healthy appearing, active young man.

This case well illustrates the problem of severe ulcerative colitis, whatever the cause. Before instituting any treatment thought must be taken not only of the etiology but also *of the amount of permanent damage to the colon.* Amebic infection, syphilis, tuberculosis, chronic bacillary dysentery, diphtheria, Balantidium coli infection, and the like may be recognized to advantage, but an extensively scarred colon is incapable of

functioning properly even after the eradication of the infection. Very often the original cause of ulceration has been supplanted by a secondary bacterial invasion. The usual medical procedures, from irrigations to rest of the colon by opium and confinement to bed, are inadequate to effect anything more than temporary relief, if indeed, they produce any effect at all. Having decided on an operative procedure, the question will arise whether anything less than colostomy or ileostomy will be effective, *i. e.*, such as appendicostomy with irrigations from above. Some long-standing and severe cases respond well to this operation, but a sufficient follow-up is likely to find them in a relapse within a few months. Again the amount of permanent damage to the colon must determine the procedure. Having performed a colostomy or ileostomy, it is the surgeon's turn to think in terms of functional ability of the colon before returning the fecal current to the normal channel. However much the patient may importune him, he should under no circumstances submit the patient to reoperation with any expectation of service from a narrowed, thickened, or permanently stiffened colon. If normal rectal or lower segment tissue remain, intestinal exclusion, with anastomosis of ileum to sigmoid, or colectomy, may be considered as a last resort. Let us now consider the less disabling infections with flagellates.

Case III.—Severe Giardia Infection.—Giardia enterica is a large flagellate which lives in enormous numbers in the duodenum, jejunum, upper ileum, gall-bladder, and ducts. From the clinical standpoint this preference for the upper intestine is the most important fact concerning the parasite, because, if it does produce symptoms, they will lie usually in the gall-bladder-ulcer group. Thus, there is a sharp differentiation between this flagellate and the two other common intestinal varieties, chilomastrix and trichomonas, which elect the colon as their habitat of preference. Absolute proof of the localization of Giardia has been gained by means of the duodenal tube, by examination of the gall-bladder removed at operation, and by autopsy, large numbers of the active flagellate

being found. A wider distribution, even to the colon, may occur in very severe cases, and with the onset of the disease, particularly in children, dysenteric symptoms occasionally enter the picture. Actual pain, vomiting, or jaundice practically rule out giardiasis. It is in chronic cases of an indefinite type, particularly with added nervous symptoms, "all gone" sensation, and an irritable intestine, that Giardia must be suspected. Having reached a certain intensity, the symptoms remain the same for many years. Healthy carriers form a fair percentage of the cases. I am indebted to Dr. H. C. Moffitt for permission to report this case from his private series.

G. M. McM., U. C. Hosp. No. 8551, thirty-two years of age, white, married, enjoyed excellent health until nine years ago. However, he recollects a few short attacks of diarrhea while in the tropics long before the present illness.

Nine years ago he began a period of obstinate constipation which lasted three years. Every type of cathartic was required, and he was languid and below par all of the time.

Six years ago, in 1916, while in the Philippines, he developed an occasional dull pain in the right side, some tenderness, indigestion, and "brain fag" in addition to his severe constipation. Appendicitis was diagnosed and the appendix removed. On leaving the hospital ten days later he developed a severe diarrhea which continued for eight weeks. No blood was passed and nothing grossly abnormal was noted about the stool. However, amebic dysentery was diagnosed after microscopic examination. Emetin was given hypodermically over a period of six weeks without any benefit. After changing his residence to another town and giving up all treatment he gradually recovered. During repeated life insurance examinations at this time no abnormality was found except a rapid pulse. His weight returned to normal with the subsidence of the diarrhea and he was soon back to his former constipated condition.

Four months later, in 1917, he lost weight again and had indigestion constantly. Nothing seemed to agree with him. Headache and dull feeling were constant, and he had some spells when he could sleep twenty to twenty-two hours a day without

benefit. There was no fever. He continued sick for one and a half years, during which time he was forced to leave the Orient and continued to be extremely nervous, irritable, and "run down." His weight was about 5 pounds below his average during this period. Anemia was found and cacodylates given. Much gas in the stomach required soda bicarbonate all of the time. Constipation continued.

By April, 1919 he was well enough to return to China, though still subject to depression and hysteria. In June, 1919 he was suddenly seized with severe diarrhea and vomiting. There were thirty or forty movements the first day, and fifteen or twenty the second. Also he had some fever. The stool did not contain blood or mucus. However, amebæ were found again, and emetin this time seemed to stop the diarrhea for a while. However, cacodylate of soda was also given during his ten-day stay in the hospital and it may have been the effective agent. Much weight was lost, and even after leaving the hospital he had to go to bed again. The bowel movements were foamy, like water, grayish, and very offensive. Gurgling sounds could be heard in the intestine. Defecation did not relieve his symptoms. His appetite failed, and sores appeared on the sides of his tongue and on the inside of his cheeks. They looked like blisters, stayed four or five days, and then went, always to return. His weight gradually dropped from 136 to 112 pounds. Doctors Birt and Blumenstock, of Shanghai, diagnosed sprue, and started treatment, under which he made a gradual and steady improvement until the summer of 1920. In spite of gain in weight, nervous trouble returned and he continued to have difficulty with his bowels. Spells of diarrhea with abnormal appearing stools, and denseness in the head which prevented thinking or talking, occurred every month or so. Castor oil, which "cleaned him out well," relieved these spells.

On October 27, 1920 he entered the U. C. Hospital. His intestines were so irritable that a little lettuce or any food containing much cellulose would start diarrhea immediately. There was a tight feeling within the abdomen which affected him all over, and also a feeling "as if he had swallowed some glass."

Tingling and heat inside often accompanied the sensation of a series of cuts. He was having two movements a day, varying from normal to grayish, and offensive. For a few hours he would feel well and then be poorly again. Exhaustion followed even slight exertion.

Family and past histories were unimportant. The physical examination was negative except for slight undernourishment, appearance of being older than thirty years, and slight generalized abdominal tenderness. The blood Wassermann was negative, with two antigens; the urine was normal. Fractional stomach analysis showed free acid up to 72 and total acid as high as 89. Screen and *x*-ray of the colon was negative. The blood showed 95 per cent. hemoglobin; reds, 5,696,000; white cells, 8200, and differential count of 66 per cent. neutrophils, 22 per cent. lymphocytes, 6 per cent. basophils, and 6 per cent. eosinophils (later 5 per cent.). Lumbar puncture showed a normal fluid, cells 2, globulin 0, protein 1, Wassermann 0.2, 0.3, 1 c.c. negative, with two antigens, and gold curve of 0012210000. Cultures from the mouth showed Streptococcus viridans predominating; no monilia were found. Repeated cultures of the stool were made by Miss J. Stickel under the supervision of Dr. K. F. Meyer in an effort to isolate Monilia psilosis. Two strains of wild yeast were grown, but no Monilia psilosis, Ashford. Cultures were repeatedly negative for organisms of the typhoid-dysentery group. A Gram stain of the stool showed more streptococci than normal, and these were easily grown in the stool cultures.

Macroscopically the stools were soft, yellowish-brown, somewhat frothy, but not particularly voluminous. All specimens contained literally billions of Giardia cysts. Also there were many large yeasts and blastocystis. No amebæ or ova were found even on repeated examination. Smears from this case stained with iron-hematoxylin are presented for your inspection. As many as eight or ten of the cysts can be seen in an oil-immersion field. All show the oval shape, four nuclei, and intricate neuromotor system which Giardia alone possesses. Absolute diagnosis can be made from the cysts in the fresh wet smear, because

no other intestinal protozoan is similar. The addition of a little iodin (Donaldson's) to the wet smear makes the neuromotor apparatus and double oval contour more evident.

Dr. W. E. Musgrave, in consultation October 29, 1920, found the history indicative of sprue, but felt that the Giardia infection could cause the diarrhea. The patient was advised to stay away from the Orient, remain on a non-residue diet, and lead a restricted life until definitely better. Attempts to eradicate the Giardia infection were begun. Early in 1921 a two weeks' course of antimony tartrate by vein was given, the technic and dosage being the same as in the treatment of bilharziasis. He improved temporarily, but the Giardia infection was no more than partially eradicated, as evidenced by the appearance of many dead "active forms" in the stool together with many cysts. Late in the spring of 1921 a five weeks' course of antimony oxid by mouth was tried, a total of 315 grains, without visible effect on the giardiasis. In the autumn of 1921 a second and longer course of antimony tartrate by vein was given, 27 grains in all, but on September 24th an enormous number of Giardia cysts were still present in the stool and he was having the same sensations inside his abdomen, with tendency to loose bowel movements, weakness, and nervousness.

Finally (late in November, 1921), he was given a series of three intravenous injections of neosalvarsan, 0.6 gram, at five-day intervals. The parasites promptly disappeared from the stool for the first time since treatment was started, and he entered a period of improvement which has continued without interruption to the present. During the spring of 1922 nervousness still required treatment, but at present (July, 1922) he is actively engaged in business again and cannot be induced to take the time for a review of the physical condition and stool. If the parasites are still absent from the stool at one year, a cure will be claimed. Clinically a great improvement is manifest.

It is noteworthy that this patient never had a bloody diarrhea and that emetin did not help him. Also no amebæ could be found in 1920 when he was still having marked symptoms.

He was always helped by arsenicals, even receiving them when being treated for sprue. These have been proved experimentally and in man to have a definite effect on Giardia. Sprue could have caused his symptoms, but absolute proof of its presence could not be obtained. Final relief resulted from treatment aimed at the overwhelming Giardia infection. Cure should not be claimed in giardiasis without sufficient follow-up, because even after a series of three neosalvarsans, relapse occurs in a considerable number of cases. Longer and more intensive intravenous treatment, or supportive treatment with rectal neosalvarsan, Fowler's solution, and cacodylates, deserves a trial. To date no other drug of the host that have been tried offers the same prospect of cure, though some have undoubted parasiticidal effect if they can be brought in contact with the flagellate in sufficient concentration. Temporary relief from sweeping out a large part of the infection by means of a strong cathartic is characteristic of flagellate infections. The problem is to reach all the parasites, and those in the gall-bladder or ducts can be reached only through the circulation. A series of negative stool examinations over a period of one year after treatment, as in amebic dysentery, should be the standard of cure.

Case IV. — Overwhelming Chilomastrix Infection. — While many doubt the pathogenicity of chilomastrix and trichomonas, cases with a heavy infection almost universally have symptoms that are referable only to the parasites. Though the chief habitat of these flagellates is the colon, in severe cases there is a spread to the upper intestine, so that treatment directed to the colon alone is ineffective. Actual invasion of the wall of the intestine with resulting ulceration is rare, if it occurs at all. The disease then is to be classed among the minor complaints and is characterized by chronicity without change in the symptoms and the absence of bloody diarrhea.

G. E. R., U. C. Hosp. No. 13,070, private service of Dr. Wm. J. Kerr, twenty years of age, single, white, first entered the hospital in December, 1921. He considered that his health

had been good until two years and eight months before, but recollected before that occasional attacks of "yellowness," always following constipation, and relieved by cleaning out the bowel with a cathartic. Then in a period of eight months he had three attacks of "distention" in the right lower quadrant, lasting three or four days. Each time he felt as though he were "swelling up" in that region, "as if he had a football inside," without other symptoms. There was no pain. On one occasion he vomited a large amount of dark brown material. Following the third attack he was told that he had appendicitis and an appendectomy was performed by a surgeon in Iowa. He was told that he had an enlarged, "black" appendix. A supplementary report was obtained that "there was no pus outside the appendix." He made a good recovery from the operation and left the hospital in ten days. However, he did not become entirely well, and during the next year and four months continually felt "all dragged out," had constipation, and developed rather frequent "side-aches" in the right lower quadrant following exercise.

During the eight months before his first entry into U. C. Hospital he became progressively worse. Much gas was belched up soon after eating, and bitter eructations together with excessive hunger would appear two or three hours after meals. His bowels were still markedly constipated. Palpitation, without dyspnea, occurred frequently, and he felt tired and below par all the time. His weight had dropped 20 pounds in two years.

His family and past histories were unimportant. Physical examination disclosed a well-developed and nourished young man. There were a few palpable glands in the carotid chain in the neck, and some fulness in the thyroid region. Abdominal tenderness was found under each costal margin, across the epigastrium, and especially on the right side as far down as the level of the umbilicus. Fractional stomach analysis showed a hyperacidity (free HCl up to 54 and total acid to 90). Gastrointestinal series showed some spasm of the antrum, and a low cecum, which was fixed and tender. The colon enema passed readily around to the cecum, which was low, drawn toward the

midline, and tender. The colon was spastic throughout, but especially the descending portion; no defects, no obstruction. The blood contained hemoglobin 100 per cent.; reds, 5,046,000; white cells, 6400, and the smear 75 per cent. neutrophils, 22 per cent. lymphocytes, and 3 per cent. endothelials. The urine was normal.

The stool on December 3d appeared normal in every way except that the microscope showed millions of chilomastrix cysts. On December 5th, 6th, and 8th there were similar findings, and, in addition, a very large number of the active flagellate, the movements having become soft following magnesium oxid by mouth. No amebæ or ova were found, and no pus or blood. The benzidin test was negative. No food indigestion was demonstrable. I have placed the smears from these specimens, stained with iron-hematoxylin, under the microscope. With the oil-immersion lens you will note that the small lemon-shaped cysts are little larger than yeasts. Each contains a single nucleus and figure-of-8 neuromotor apparatus. The size, shape, and internal structure of these cysts is so uniform and characteristic that absolute diagnosis can be made from them. None of the common intestinal flagellates or amebæ present anything even remotely resembling them.

On December 6th there was a sharp rise in temperature to 38.2° C., with a trifling rise on the three following days. Discomfort and soreness all over the abdomen, slight nausea, and headache accompanied the fever. Physical examination was the same as at entry.

Although fever and abdominal pain were not characteristic of chilomastrix infection, no other definite source could be found for the spastic colitis. Consequently he was given 5-minim capsules of Oleum terebinth four times a day for two days, beginning on the afternoon of December 9th. The parasites promptly disappeared from the stool and the patient was symptomless and much better for nearly ten days. Stool examinations on December 19th and 24th were still negative for the parasite. However, during the latter part of December he felt poorly again, tired easily, lost his appetite, and had several attacks of

pain in the right side of the abdomen, with radiation to the right chest. The pain started as a throbbing sensation in the right lower quadrant, was spasmodic, and ran up directly into the chest without radiation to the back. Headache was present daily for a week before his second entry into the hospital on January 3, 1922. Also he had a slight afternoon fever (0.5° C.) for three days before entry. Physical examination was essentially the same as at the previous entry. The cecum and ascending colon were palpable. The right side of the abdomen was tender to deep pressure from the costal margin to McBurney's point. The patient complained of nausea when pressure was applied over the tender area. This time the greatest tenderness was high in the right upper quadrant. However, he was not tender at Mayo-Robson's point or at the level of the tenth rib in the posterior axillary line. Liver dulness extended 2 fingerbreadths below the costal margin, the edge being smooth and a little tender. The spleen could not be felt; the descending colon was palpable and somewhat tender. Rectal examination was negative.

The urine now showed s. p. t. of albumin, but was otherwise negative. The stool again contained an enormous number of chilomastrix cysts. The blood was almost exactly as at previous entry. A Lyon's test was done on January 6th, and bile obtained in I and II, while III and IV were colorless. Numerous Streptococcus viridans, a few Bacillus coli, and Staphylococcus albus were obtained by culture from I and II. Proctoscopy was essentially negative, one small area of punctate hemorrhage being noted. Von Pirquet test with both human and bovine tuberculin was negative at twenty-four, forty-eight, and seventy-two hours. A second Lyon's test was done on January 17th. Fasting duodenal content and tubes I, II, and III were all strongly colored with bile and contained a little mucus. Microscopically a few bacteria and occasional pus-cells were seen. Cultures gave a few yeasts and few S. albus in the fasting stomach contents, no growth in the fasting duodenal content, a few B. coli in Duod. I, numerous B. coli in Duod. II, and numerous B. coli and a few non-hemolytic streptococci in Duod. III.

The stool flora was slightly proteolytic; B. welchii numerous. Culture was negative for bacteria of the typhoid-dysentery group. Later urine examinations were negative for albumin. The temperature reached 37.4° C. on one day, but was normal the rest of the time.

Again the feeling was that chilomastrix alone could not cause the symptoms. Postoperative adhesions with tying down of the cecum were considered the most probable condition. Gall-bladder disease did not seem to be entirely ruled out. However, the parasites were evidently present in enormous numbers and the patient had been practically symptomless for a while after partial eradication. Turpentine by mouth plus iodin irrigations of the colon after the method of Escomel had been tried again, but without success, even under supervision in the hospital. Therefore on January 19th a change was made to Fowler's solution in the usual ascending dosage, to be continued for a month at least. Three stool specimens (two of them soft) examined on February 6th were negative for chilomastrix. On February 13th the stool was still negative, and again on February 20th no parasites could be found. Meanwhile the patient had begun a period of betterment which has continued without interruption. At present (July 28, 1922) he is active, robust, and symptomless. Because uncomplicated chilomastrix infection is rare, an attempt will be made to examine a series of stools one year after treatment. If all are negative, a cure will be claimed. Clinically a remarkable improvement has taken place.

In closing let me emphasize the importance of routine stool examination, and the value of adherence to a few sensible procedures that greatly simplify the examination of feces and at the same time lessen the disagreeable nature of the task. The entire specimen is rarely needed. A portion equal in volume to a walnut (2 x 3 cm.) and taken from the softest part of the stool is sufficient for routine examination. Placed in an air-tight container, such as a corked bottle, the specimen should be sent immediately to the laboratory and examined at once. Active amebæ disintegrate often within fifteen minutes. Active

flagellates, strongyloides larvæ, and pin-worms cannot be found in old stools, nor can the flora be studied. The best way is to arrange for the collection of specimen right in the laboratory. The importance of examining the specimen while fresh cannot be emphasized too much. In general, if a protozoan parasite is the source of the symptoms, it will be present in great numbers in the stool. Mixed infections are common, and for that reason pathogenicity should not be assigned to one of the minor parasites until the major varieties, such as Entamæba dysenteriæ (histolytica), have been ruled out by repeated examination. An irreducible minimum of procedures in examining the stool is:

1. Gross appearance—in regard to color, mucus, blood, or pus.
2. Examination of wet smear for excess food, amebæ, flagellates, ova, pus, blood, balantidium, and spirochetes.
3. Same after addition of iodin (5 per cent. KI in salt solution, saturated with iodin) for starch residue, and to bring out the characteristics of cysts, if present.
4. Benzidin test for occult blood.

Upon sufficient indication may be added:

5. Iron-hematoxylin stain (quick method) for identification of parasites when present.
6. Brine loop concentration test for ova (Kofoid).
7. Gram stain of flora.
8. Culture for typhoid-dysentery, or other group, or for yeasts and molds.

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CLINIC OF DR. EUGENE STERLING KILGORE

ST. LUKE'S HOSPITAL

SYPHILITIC AORTITIS

History. Clinical Characteristics with Illustrative Cases. Tendency of the Disease to Latency and Consequent Difficulty of Early Diagnosis. Variability of Early Symptoms, Including Extrathoracic Symptoms. Importance of *x*-Ray in Early Diagnosis. Prognosis. Treatment.

CHRONIC inflammatory disease of the aorta, especially of the arch, with thickening and stretching of the walls and tendency to damage the aortic valve has been recognized clinically for more than a century since the studies of Scarpa and of Hodgson. The somewhat similar effects of advanced senile changes at first obscured the picture of the inflammatory disease; and as to the relative importance of different infectious agents in etiology opinion is still uncrystallized. Syphilis has been clearly recognized as an important factor since the publication in 1875 of the work of the English physician, Francis H. Welch,[1] and in recent years many demonstrations of spirochetes in these aortic lesions have further emphasized the frequency of syphilis as a cause. That it is the most frequent cause is now pretty generally believed, and especially in Britain and America many regard it as almost the exclusive agent. Continental writers attribute many cases to rheumatism, scarlet fever, influenza, typhoid, and other infections. A survey of the modern literature leaves one with the impression that undoubtedly numerous infections may leave their marks in this place with considerable frequency, but that in middle-aged subjects the appearance of clinically recognizable aortitis with its characteristic tendency to involve the aortic valve or to produce aneurysm or angina

should for practical purposes be accepted as presumptive evidence of syphilis. The more carefully such cases have been studied both clinically and pathologically, the higher have been the percentages of syphilis reported. Syphilis is always difficult to "rule out." Too often where other etiology is apparent an underlying syphilis is missed. The following is an illustrative case:

Case I.—An intelligent blacksmith foreman, of healthy Scotch ancestry, with no knowledge of venereal infection, and, in fact, with a clear health record except for rheumatism in boyhood, was still, at the age of forty-six, in excellent physique and a good amateur boxer. His first symptom occurred while "punching the bag" three months before our examination, and was described as an uncomfortable tightness or constriction of the abdomen and chest—as if his "wind was cut off." In the next few days similar but minor sensations were felt on stair climbing; and then he went to his doctor, related the negative venereal and positive rheumatic history, learned that his heart leaked, and went home to take rest and digitalis. His downward progress was not retarded by this treatment or by many subsequent paid-in-advance manipulations of the spine. In succession there followed increased substernal distress and dyspnea on exertion, forced retirement from work, orthopnea, cough, and flatulence.

Our physical examination brought out the typical signs of aortic insufficiency—"heaving" impulse, with extension of apex-beat outward and downward (enlarged left ventricle); some paramanubrial dulness, with pronounced pulsation in suprasternal notch (enlarged arch); questionable inequality of carotids (unequal involvement of orifices from aorta?); diastolic murmur along the left sternal margin, slight systolic whiff without thrill in the neck, and absent aortic second sound (advanced deformity of valve); and the peripheral signs of water-hammer pulse, systolic flushing of the skin, to-and-fro murmur, with compression of the femoral artery (Duroziez), increased pulse pressure (systolic 160, diastolic 75). *x*-Ray

showed enlarged heart of aortic type and bulging of the aortic arch, especially the ascending portion. Electrocardiogram showed the prominent R-I and S-III of left ventricular preponderance. Wassermann test strongly positive; slight secondary anemia and a little albuminuria. He died a few weeks after starting antiluetic treatment.

The disastrous result of tardiness of diagnosis and treatment in this case is not exceptional. Syphilitic disease of the aortic valve is notoriously difficult to treat successfully; and while the nature of the invasion (early choking of coronary arteries, simultaneous invasion of heart muscle, etc.) may be partly responsible, the chief factor is undoubtedly the headway that is usually allowed the disease before it is efficiently combatted. In many, perhaps most, instances considerable headway is inevitable, for the reason that the invasion is silent and the disease is advanced before the patient seeks examination.

Case II.—A young woman being treated for luetic iritis, as part of a general diagnostic study, had *x*-ray examination of the chest. Dr. J. M. Rehfisch, who knew nothing of her lues, recorded his strong suspicion of this infection as soon as he saw on the screen and 2-meter plate (Fig. 62) the dilated ascending part of the aortic arch—and yet there were no chest symptoms, and no physical signs of aortitis could be found either before or after the *x*-ray had revealed it.

Case III.—Another instructive recent case was one of Dr. J. M. Read's. A man aged fifty-seven, with history and examination suggesting nothing but duodenal ulcer, during *x*-ray study (which confirmed the ulcer diagnosis) was observed to have the suspicious bulging of the first part of the aorta. The Wassermann test was then found strongly positive, and on reexamination a slight systolic murmur was found in the aortic area. Cases to be described below will further illustrate the silent invasiveness of the disease as shown by the advanced lesions present when symptoms first appear.

These observations are in harmony with the fact long recog-

nized by pathologists that syphilitic aortas frequently are found unexpectedly in subjects who die of other causes. Eich,[2] in his pathologic study of 63 cases of syphilitic aortitis, reports that about half of them had neither signs nor symptoms of the

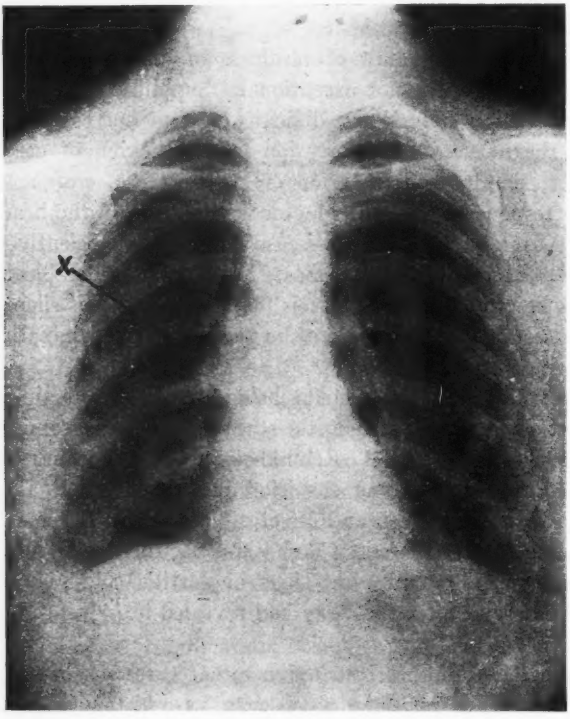

Fig. 62.—Two-meter chest plate, Case II. At *x* note the slight bulging to the right of ascending aorta without noteworthy changes in aortic shadow to left of sternum.

disease during life. Longcope[3] and others have made similar reports. In fact, in autopsy studies on syphilitic subjects the vast majority have been found to have specific lesions in the aorta (Warthin[4]), while, of course, comparatively few have the diagnosis made during life.

How soon after the chancre infection of the aorta *usually* occurs is not known. Few cases are recognized until several or many years later, but advanced and fatal ones have been seen within a few months after infection, and Brooks[5] observed one such before the roseola had faded. It cannot be doubted that many more such early cases exist than can be recognized clinically; and, in view of the autopsy studies above referred to, it is fair to regard the aorta as a common (perhaps the most common) residence of the spirochetes during the years of "latency."

It is clear then that the mere existence of syphilis, especially acquired tertiary syphilis, throws considerable suspicion on the aorta as a site of the infection. But, on the other hand, as in our first-mentioned case, it is precisely where the suspicion of syphilis has not occurred that the early recognition of aortic involvement is most important; and it is now in order to consider the clinical data available for such diagnosis.

Symptoms.—According to the direction and extent of the pathologic process the symptoms vary widely under three main headings—aneurysmal, anginal, and those of circulatory failure. Saccular aneurysm with its varied pressure phenomena is essentially a late stage and may be omitted from a discussion of early manifestations. Simple fusiform aneurysm in the sense of more or less diffuse dilatation is usually present before diagnosis is possible, but its early symptoms are those of angina or associated heart weakness rather than pressure.

The anginal symptoms vary from the mildest ("anginoid") sensations to the most severe forms, and are not distinguishable from those of angina of other etiology.

Vague discomfort or actual pain is the most common first complaint. The occasional subject who describes an abrupt onset with severe angina may, if carefully questioned, remember preliminary minor transitory attacks. A dull pain, or "gripping" or "drawing" sensation beneath the sternum, brought on or increased by exercise or excitement is common, but the kind and the location of pain are quite variable. Pain over the heart is less common than substernal pain, and is much more

characteristic of pseudo-angina. One or both shoulders or arms, especially the left arm, forearm, and ulnar distribution in the hand, the neck, jaw, abdomen, or back may be directions of pain radiation or less often original sites.

Case IV.—A mechanic aged thirty, with well-developed aortitis and aortic insufficiency, strongly positive Wassermann,

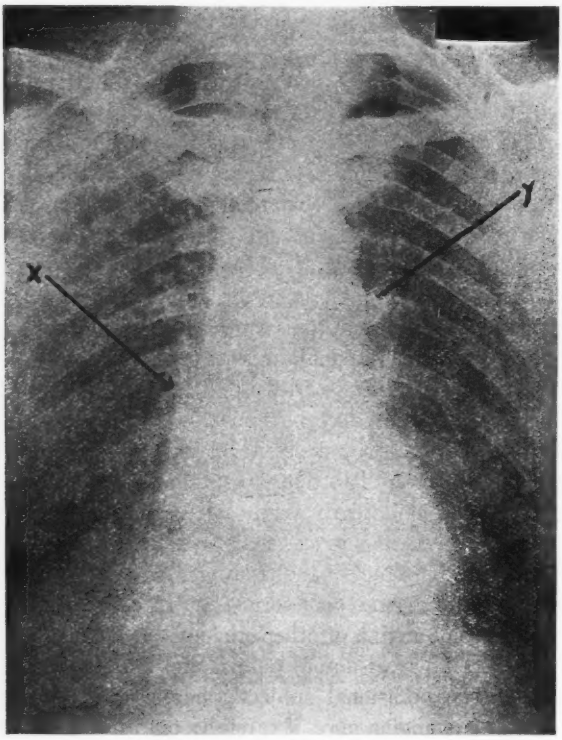

Fig. 63.—Two-meter chest plate, Case IV. Bulging of ascending aorta at *x*, and some diffuse increase in aortic shadow at *y*.

and the usual luetic aortitis *x*-ray picture (Fig. 63), complained solely of a sharp pain between the shoulder-blades on exertion.

This had been present two months; and there can be no doubt it was associated with activity and progress of the aortic lesion, since the Wassermann test and physical findings had been entirely negative a year previously (on account of an old tibial infection, a competent internist had then gone over him looking especially for luetic stigmata).

Case V.—A railway flagman, aged fifty-one, had complained for five months of vague abdominal distress, with constipation

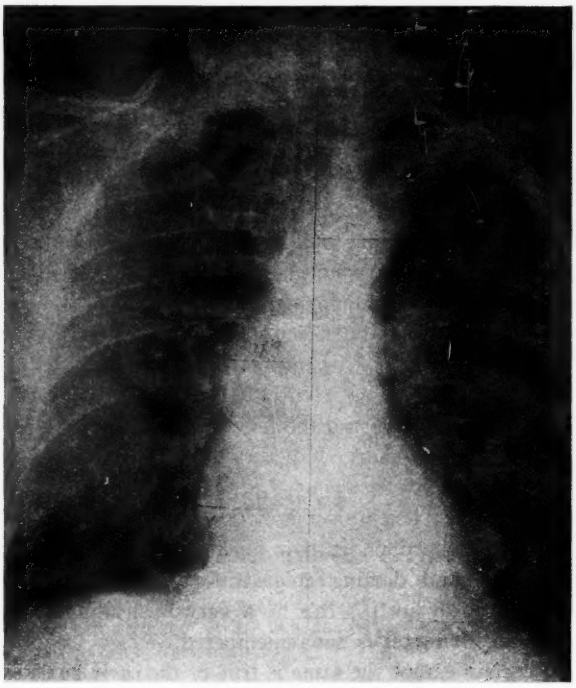

Fig. 64.—Two-meter chest plate, Case V. Note enlargement of entire aortic arch.

and positional pain (could not lie on left side) under left costal margin. There was no indication of syphilis in the history

or physical examination. Wassermann test was moderately positive. In the course of *x*-ray studies of the gastro-intestinal tract and spine (both negative) an enlarged aortic arch was observed (Fig. 64), and the abdominal symptoms disappeared with antiluetic treatment. Whether or not they were referred from the aorta is a question of more theoretic than practical importance.

Case VI.—An overweight clerk, aged fifty-two, with negative luetic history, has complained in the last six weeks of a "darting" momentary pain shooting straight through from side to side 3 or 4 cm. below the level of the ensiform, felt only when lifting his invalid wife in a very strained position—a thing he has done for years before without discomfort. Two or three times a week he is late for his commuter's train, and runs for it the last block or two with positively no pain or any other distress except what he regards as very ordinary "puffing" for a man of his age and build. I thought I detected slight increase of retro- and paramanubrial dulness, and the subclavian pulsations were rather prominent; but a more definite suggestion of aortic trouble was the accentuated and "metallic" aortic second sound associated with normal blood-pressure. Physical examination was otherwise essentially negative, but the Wassermann was triple positive and the teleoroentgenogram and screen examination showed marked dilatation affecting at least the whole arch (Fig. 65).

These 3 cases illustrate some of the less common types and kinds of pain—sharp effort pain in the back, pain in upper left quadrant, and darting epigastric pain on lifting. Evidently the pain of aortitis can be a very misleading symptom if its variable character is not remembered.

To a certain extent the same is true of the *early* heart symptoms, which may appear in the absence of pain. Marked dyspnea, continuous or paroxysmal, orthopnea, periodic breathing, edema, etc., are familiar late events which need not be dwelt upon here. Their appearance is usually but not always delayed until after aortic leakage is demonstrable. Minor symptoms

of heart weakness, on the other hand, are quite often encountered before the aortic regurgitation. There may be premature "general exhaustion" from exercise or a little undue breathlessness on exertion, especially after meals. Vague symptoms referred to the stomach probably belong in this category, espe-

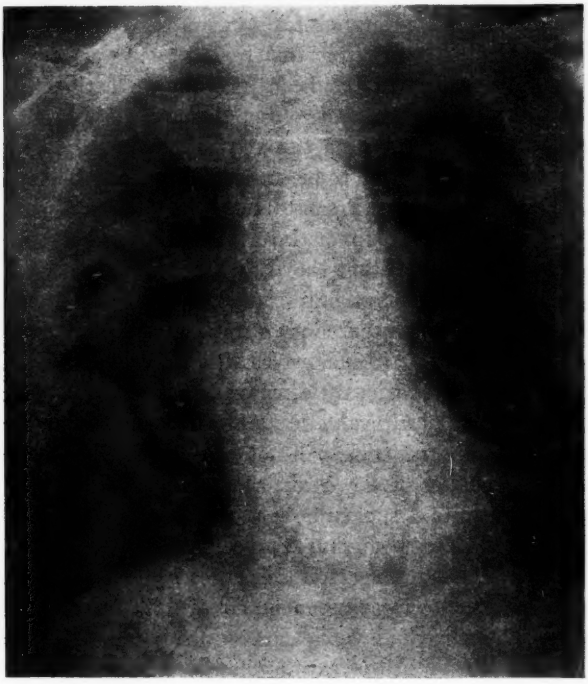

Fig. 65.—Two-meter chest plate, Case VI. Diffuse dilatation of arch. Resembles senile aorta, but occurs in a man of fifty-two with normal blood-pressure and positive Wassermann.

cially complaints of "gas," with or without belching, epigastric "tightness," "fulness," or nondescript discomfort—all of these being usually more prominent after meals and exercise. Two of our patients when first seen had been treated several months for "stomach trouble," and another, seen with Dr. Lewis H.

Young, which he had recognized from the outset as syphilitic aortitis with regurgitation, had at first complained of stomach fulness, anorexia, etc. These symptoms have been much slighted in the literature. They really deserve considerable emphasis, not that they are decisive in diagnosis (they are common also in the incipient heart breakdowns of hypertension, arteriosclerosis, etc.), but because as early symptoms they are apt to misdirect attention away from the circulatory system.

Disordered action of the heart may be an early effect of syphilitic invasion. One of our patients had "palpitation attacks" which proved to be paroxysmal tachycardia. Heart-block has long been known to be caused occasionally by syphilis. Fibrillation may occur. Premature contractions are common, but they are also so common in other conditions or with no known pathology at all that they have little importance except to suggest the need for general examination, and the question of syphilis should be in the mind of the examiner.

Now these irregularities as well as the beginning symptoms of heart weakness previously discussed are about as likely to appear before the aortic valve leaks as afterward, so that mere extra work for the ventricle will not account for them in most instances. Choking of the coronary arteries by the syphilitic process in the aorta is spoken of as a cause, but the correlations of clinical and autopsy findings have not borne out this idea consistently. That the heart muscle itself is diseased is further suggested by the downward tendency of syphilitic aortic disease as compared with equal valve damage in a healed rheumatic case. Warthin,[4] by use of extraordinarily exhaustive methods of pathologic search, finds spirochetes in the heart muscle in most cases of syphilitic aortitis; and, in the light of the clinical facts, one cannot help suspecting that those who fail to confirm his results have not hunted with the same persistence.

Physical Signs.—The signs referable to aortic regurgitation have been mostly mentioned in our first described case. They are familiar and need not detain us. When uncomplicated by mitral disease they appear "out of a clear sky" in a middle-aged person they should be regarded as indications of syphilis

until proved otherwise. But a mitral regurgitant murmur is common with uncomplicated aortic disease, due to stretching of the mitral orifice, and it may be impossible to differentiate with certainty this condition from an associated mitral endocarditis. Aortic stenosis resulting from syphilis is rare (some have denied its existence) and cannot be assumed on account of finding systolic murmur and thrill in the neck unless definitely confirmed by a plateau pulse.

Saccular aneurysm with its varied pressure signs is essentially a late manifestation and must be passed over. It is well to remember, however, that aneurysms of considerable size may be not only painless, but devoid of the usual signs. I have seen an undoubted *x*-ray of thoracic aneurysm the size of a tennis ball for which neither I nor my colleagues could find dulness or other signs even after we knew it was there.

The earliest physical signs of the disease depend upon stretching, thickening, and stiffening of the aortic wall. One may find the mild pressure effects of dilated neck veins or the pulsations of tortuous carotids, prominent subclavian and suprasternal pulsation associated with upward displacement of the arch. High diaphragm, senile changes, displacement of aorta due to hypertension or character of the heart thrust (thyroid or nervous heart) should be ruled out. Inequality of carotid pulsations may occur through predominating pathology in the region of one orifice from the aorta. Tenderness in the suprasternal notch may be found in acute cases. Pulsation beside the manubrium, especially on the right, is a valuable sign, which with a good cross-light can be seen better than felt. Dulness over and beside the upper sternum, especially in the first spaces, is important. The lateral dulness should be examined for with a small plexímeter like the end of a finger advancing from the sides toward the sternum in one interspace at a time.

Aside from the diastolic aortic regurgitant murmur, when present, the most important auscultatory sign is the modified second sound in the aortic area. When typical it is highly characteristic, and is variously described as "ringing," "metallic," "tympanic," etc. Potain calls it "*le bruit de tabourka*" from its

resemblance to the note of the Arabian earthen kettle-drum. It is unlike the simply loud aortic second sound of hypertension, and it may be well marked without increase of blood-pressure. Its resemblance to the note of the tabourka may be due to the fact that both derive their peculiar timber from the thick rigid walls supporting the vibrating diaphragm—the approximated cusps of the aortic valve, on the one hand, and the skin drumhead on the other. The bruit de Tabourka may be felt with light palpation ("diastolic shock"). It develops gradually when the process of thickening, stretching, and stiffening of the aortic wall has made considerable progress; and it may, of course, disappear if the aortic valve becomes too badly crippled.

Fever in our experience has occurred in only 1 case, which at autopsy was found complicated by micotic endocarditis; but most of our cases have been ambulatory and lacked consistent temperature records. Fontain[6] reports fever as common, while Allbutt[7] considers it rare.

x-Ray Examinations.—Unfortunately, all these signs depend for their production upon the existence of lesions pretty well advanced. Considerably earlier lesions are often brought to light by *x*-ray studies. And, since the Roentgen method properly used practically never fails to show aortitis for which there are any physical signs, and since it often saves us from misinterpreting signs, it is by far the most important means at our command for the diagnosis of aortitis. I am not one of those who belittle the *x*-ray and use it sparingly and grudgingly. I do not follow our prophets who see false gods in every laboratory, and especially the radiographic laboratory, and who lament an alleged latter-day apostasy from the true worship of physical signs. Those who seek the laboratory report as a refuge from the work and thought involved in physical examination could not, in my opinion, be converted to the communion of the faithful by merely cutting off their laboratory contacts. They and their patients would be still worse off without the aid thus afforded. And even if it were true that percussion and auscultation had deteriorated on account of the prevalence of *x*-ray examinations (they have, on the contrary, been bettered

by comparisons with *x*-ray results, especially the limitations of percussion are better understood)—even if the worst were true, resistance to the use of *x*-rays would be no less quixotic than would be an objection to the practice of inspection for the reason that it damages our palpation, since the blind are known to develop superior tactile sensibility. The trouble is that the *x*-ray is used not too much, but too little. If every doctor could carry about the apparatus and use it as conveniently and freely as his stethoscope or ophthalmoscope, there would be no more opposition. The practically unavoidable but none the less unfortunate splitting off of roentgenology into a separate specialty results in narrowness of view and diagnostic failures which could be avoided by better liaison with the clinicians. To illustrate this point one has only to picture to himself the absurdity of, let us say, percussion practised as a specialty, and the "percussors" furnishing "diagnoses" based exclusively upon their work. The remedy lies in freer general use of *x*-rays and more intimate contact and co-operation between clinicians and roentgenologists.

I make this digression apropos of the diagnosis of aortitis because some prominent clinicians still speak of the *x*-ray as if it were simply "occasionally" of some value in the study of these cases, but, in general, of minor importance, if not a positive hindrance, to the examiner. We need not debate their diagnostic abilities. The problem of finding these cases early enough is one for the average practitioner, and I, who claim average skill, would miss many early cases if not for the radiographs which I use on the slightest pretext.

The characteristic *x*-ray picture of syphilitic aortitis shows simple bulging of the ascending limb of the aortic arch visible to the right of the sternum just above the curve of the right auricle. Figures 62–65 are examples. These are "2-meter" plates (target 2 meters away from plate), which we always take unless we have orthodiagrams. Without this care to secure approximately parallel rays there is great distortion in the shadows of intrathoracic objects, which varies with the thickness of the subjects. Dr. Rehfisch also, however, always screens our patients in the usual way, and finds that in some of the

earliest cases a hint of the trouble in the root of the aorta is obtained in the exaggerated screen picture, which fades into the spinal column shadow in the 2-meter plate. The hypertension aorta, which often shows a similar shadow to the right

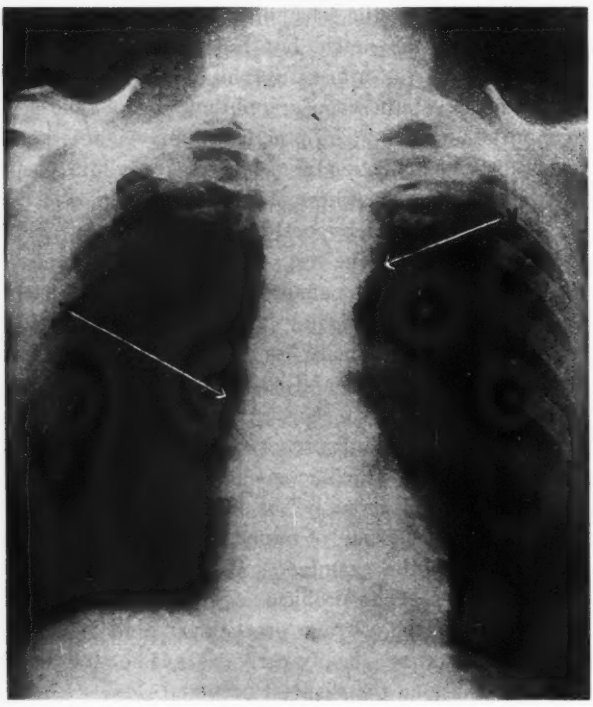

Fig. 66.—Two-meter chest plate of a subject with chronic hypertension. While at *x* it shows extension of aortic shadow to the right, as in syphilitic dilatation; at *y* is the exaggerated knob-like projection indicative of distortion in the curve, which accounts for the shadow at *y*.

due to elongation and distortion of its curve, can usually be recognized by the exaggerated rounded knob-like shadow to the left of the manubrium where the vessel plunges backward. This is shown for comparison in Fig. 66. The senile sclerotic aorta also bulges to the right, but since the process is more

diffuse along the aorta it usually presents diffuse bulging above and to the left. There are, of course, many intermediary pictures not thus clearly classifiable, and there are *x*-rays which receive different interpretations from those indicated above when, as, of course, is always necessary, they are compared with other clinical findings. Figure 65, for example, would illustrate well the diffusely dilated senile aorta if it did not occur in a middle-aged man with positive Wassermann test and a "tabourka" aortic second sound associated with normal blood-pressure. His aortitis is one of the less common kind which extends over the arch and at least part way down the descending limb.

The **Wassermann reaction** has been reported positive in from 60 to 95 per cent. of cases. Probably it is present at some time in every case; but the important practical point is that at a given examination it may be negative in an undoubted case of luetic aortitis. Warthin reports finding spirochetes in the aorta or heart of subjects who during life had a negative reaction. And we have already mentioned a case of aortitis with strongly positive reaction who had a negative reaction one year previously. The aorta in this case may have been invaded in the year between the two tests, but it is more probable that the infection was latent in the aorta at the time of the first examination. McCrae[8] mentions a case considered for years to be one of non-specific aortitis in whom the syphilitic diagnosis was finally made from the spinal fluid.

Prognosis.—Length of life after the onset of symptoms is usually given as from a few months to two or three years, but patients may live and work for many years. No definite figures are available to show how much the outlook can be bettered by adequate treatment begun early. Probably the effect of such treatment in prolonging life and usefulness is considerable. Those exhibiting heart weakness have a distinctly poorer outlook whether or not the aortic valve is crippled. Sudden deaths are common and are, in all probability, often due to fibrillation of the ventricles. On one occasion I examined one of these subjects within about ten or fifteen seconds of the instant when

he fell while strolling about the hospital ward, and was unable to detect either heart sounds or pulse.

Treatment.—There is a wide-spread feeling of hesitancy about applying vigorous antiluetic treatment, especially with arsenicals, in these cases. We still take the view that the disease itself is so deadly and the necessity so urgent of endeavoring to stop its progress that intensive treatment is justified. We begin with mercury in the hope of avoiding a possible Herxheimer reaction; then follow with minimal doses of neosalvarsan (0.2 gm.), and gradually increase at five-day intervals up to 0.9 gram. The 3 fatalities during treatment we have had have all happened during the early period of light treatment. After a month of neosalvarsan treatments we go back to mercury rubs or injections for a month, and thus alternate month by month for six months. Ordinarily the patient then rests from all treatment in the next half-year, then takes a second six months' course like the first, and thereafter remains under observation without further treatment unless developments suggesting further syphilitic activity occur. Potassium iodid in small or moderate doses is prescribed during the periods of other treatment.

Cases showing marked heart weakness should have the usual attention to rest in bed in a semi-elevated position so far as possible, limitation of fluids, easily digestible diet, with small frequent feedings to avoid stomach distention, mild cathartics if necessary, and morphin or other hypnotic if necessary to secure sleep. Digitalis is not contraindicated and is of some value, though less so than the general measures, and less in these cases than in decompensated rheumatic hearts.

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CLINIC OF DR. SAMUEL HURWITZ

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BACTERIAL ASTHMA IN CHILDREN. THE RÔLE OF INFECTION AND THE VALUE OF VACCINE TREATMENT

PERHAPS no group of sufferers has so greatly benefited by the recent advances in our knowledge of the causes and treatment of asthma as have the children. And in this clinic, even at the risk of trespassing in the field of the pediatrist, I have chosen to present to you the clinical course of 3 children who demonstrate the hopefulness of treatment directed against a certain form of asthma in the child.

In children the type of asthma which has received the greatest attention from most observers has been the form in which hypersensitiveness to some protein, food, animal, or plant, has been found to be the chief etiologic factor. This is not the type of asthma which I am going to discuss at this time. The group which these children represent is one in which infection has been found to play the major rôle in the production of the symptoms. This form of asthma has been very appropriately designated in recent literature as asthmatic bronchitis. To be sure, as I shall tell you later, it is not conceded by all authoritative clinical observers that bacterial invasion of the respiratory tract or that the presence of bacteria in other foci will in itself give rise to this type of asthma. However that may be, experience, both with adults and with children, has taught us to place great confidence in the value of vaccines properly prepared from these bacteria and properly administered. Vaccination has been found to be a considerable aid in giving relief to

these sufferers over a shorter or longer period of time, and in some instances in bringing the asthmatic paroxysms to an almost complete arrest.

These 3 patients, selected from a considerable number, in the main, adults, bring out the chief historic points in the development of this form of asthma, and indicate the mode of directing effective treatment against the causative bacteria by the employment of autogenous vaccines.

Case I.—The first child, a boy of ten, first consulted me on September 8, 1920. The family history of this boy is of considerable interest in view of the presence of hay-fever in the father, a tendency to bronchitis in the mother, and eczema in a younger sister. The child was a full-term baby, for the most part breast fed, with supplementary feedings of cow's milk. No idiosyncrasies to the common foods were noted by the mother. Before the age of three the boy showed a great tendency to catch cold easily. These colds were attended by rhinitis, and were followed at intervals of two to three months by slight spells of wheezing. Between the ages of three and nine these spells ceased entirely. A tonsillectomy was done at the age of nine as a prophylactic measure. The following year, at the age of ten, the patient had a moderately severe attack of influenza, complicated by bronchopneumonia, lasting several weeks. After this respiratory infection the asthmatic seizures began to recur at intervals of two to three months. At times the spells would last a week, the characteristics of each paroxysm being more or less the same. Inspiration has been found more difficult than expiration. The chief contributing causes have been catching cold, the inhalation of dust, overexertion, usually attending play, and overeating. There has been no definite association of the attacks with food, animals, or plants. Treatment in the past has consisted, in the main, of general hygiene, careful diet, deep breathing, osteopathic treatments, iodids, and codein.

On examination, the patient was found to be well developed and well nourished for his age. No foci of infection could be

made out by a careful search of the sinuses, nasopharynx, and teeth. The thorax was quite markedly increased in the antero-posterior diameter and the sternum was a little protruding. The lungs showed signs of chronic distention, marked hyper-resonance, and immobility of the lung borders. The respiratory murmur gave evidence of bronchospasm—prolonged expiration and many sibilant and sonorous râles. The right border of the heart was perhaps a little further beyond the right sternal margin than one would expect in a child of the patient's age. In every other particular physical examination was negative. A fluoroscopy of the chest showed nothing remarkable, and routine examinations of the blood and urine were negative.

Protein sensitization tests were carried out by the cutaneous method with the common foods, animal emanations, pollens, and bacteria. Only two of the bacterial proteins—Staphylococcus albus and citreus—gave questionable reactions.

Three cultures of the sputum, carried out by a method which I shall comment upon later, showed the presence of two predominating types of streptococci—non-hemolyticus and viridans—and Staphylococcus aureus. A vaccine prepared by subculturing these three organisms was made up in such strength that 1 c.c. contained 1,000,000,000 of the mixed organisms in about the proportion of their prevalence in the cultures. For purposes of conciseness I have given the treatment of this and the other patients in tabular form (Table 1).

Summary and Clinical Course.—This patient has a familial asthmatic background, but shows no evidences of sensitization to a protein himself. Asthma, in this instance, followed a definite tendency to respiratory infection beginning at the age of three, and subsequently became full-blown after an attack of influenza at the age of nine. Repeated paroxysms at intervals of two to three months had produced definite evidences of pulmonary emphysema.

Two courses of treatment with autogenous vaccines, each one carried out for a period of about four months, resulted in relief. This was attained not only during the period of immunization, but for a considerable time subsequent to the last treat-

Table I. Treatment Record. Case I. A.M. Age 10. Diagnosis, Bacterial Asthma

Date.	Dose of Vaccine	No. of Bacteria (millions)	Reaction Local	Reaction Constitutional	Clinical Condition & Remarks
Sept.17,1920:	0.2 cc	200	0	0	
Sept.24,1920:	0.3 cc	300	0	0	
Oct. 1,1920:	0.4 cc	400	0	0	
Oct. 8,1920:	0.5 cc	500	0	0	
Oct. 15,1920:	0.5 cc	500	0	0	
Oct. 27,1920:	-	-	-	-	Severe asthmatic paroxysm began yesterday following a cold in head with rhinitis. Adrenalin (1-1000)12 minims.
Nov. 19,1920:	0.1 cc	500	0	0	New vaccine prepared of mixed sputum bacteria.
Nov. 26,1920:	0.2 cc	1000	0	0	Plays football daily without bringing on asthma.
Dec. 1,1920:	0.3 cc	1500	0	0	Condition excellent.
Dec. 4,1920:	0.4 cc	2000	0	0	Has had coryza for past few days, not followed by asthma as formerly.
Dec. 10,1920:	0.5 cc	2500	0	0	
Dec. 15,1920:	0.65	3250	0	0	Condition excellent.
Dec. 20,1920:	-	-	-	-	Treatment interrupted on account of chickenpox.
Feb. 1,1921:	-	-	-	-	Condition excellent. No asthma since Oct.27;weight 90 lbs.
Sept.30,1921:	-	-	-	-	Slight attack of asthma in July; severe attack today;both from exposure and colds;attacks very short lasting only a day.
Oct. 14,1921:	0.1 cc	100	0	0	New vaccine prepared. Contains non-hemolytic streptococcus and streptococcus Viridans.
Oct. 22,1921:	0.15 cc	150	0	0	Weight 98 lbs.
Oct. 28,1921:	0.2 cc	200	0	0	Condition excellent.
Nov. 4,1921:	0.3 cc	300	0	0	Had spell of asthma on day following treatment- duration several days.
Nov. 11,1921:	0.1 cc	100	0	0	
Nov. 18,1921:	0.2 cc	200	0	0	
Nov. 25,1921:	0.25 cc	250	0	0	
Dec. 2,1921:	0.3 cc	300	0	0	
Dec. 9,1921:	0.3 cc	300	0	0	Has had cold in head but no asthma.
Dec. 16,1921:	0.4 cc	400	0	0	Cough better; no asthma.
Dec. 23,1921:	0.5 cc	500	0	0	
Dec. 30,1921:	0.55 cc	550	0	0	
Jan. 6,1922:	0.5 cc	500	0	0	
Jan. 13,1922:	0.6 cc	600	0	0	
Jan. 20,1922:	0.6 cc	600	0	0	Weight 108 lbs.
Jan. 27,1922:	0.7 cc	700	0	0	General condition excellent. No attacks of asthma for three months.
Aug. 15,1922:	-	-	-	-	Has had occasional colds in head and rhinitis but no asthma since last treatment in January.

ment, six months having already elapsed without a paroxysm. How much longer the patient will continue free remains to be seen.

Case II.—The second patient, R. T., a boy of eight, was first seen in March, 1921. This boy was a full-term baby and bottle fed. The mother had never noticed that the child had

any idiosyncrasy to any form of food. In fact, the first two years of life were quite free of illness. At the age of two the tonsils and adenoids were removed without good cause. When three years of age the patient began to show a tendency to colds. These were accompanied by fulness in the head, running from the nose, and slight cough, and would recur at intervals of about six months. An examination by a pediatrist at this time showed evidences of asthmatic bronchitis. During his fourth year the patient passed through an attack of whooping-cough lasting three weeks. Following this illness the colds occurred at about the same intervals, but with greater severity. In 1918, during the first wave of influenza, the child, then about six years of age, contracted the disease and was very ill for three weeks; fever, cough, and delirium were pronounced. Six weeks following this he was again taken ill with bronchopneumonia and was in bed for several weeks. It was three weeks after his recovery from bronchopneumonia that the patient had the first violent asthmatic paroxysm. These spells continued with varying severity and at intervals of about six months until 1920, when they became more frequent. The patient would rarely go longer than two and a half to three months without a paroxysm. The average duration of each attack has been three to seven days. Prior to treatment with vaccines counterirritation to the chest and cough mixtures had been the chief therapeutic measures employed for the paroxysms.

Examination showed that the child was shorter, thinner, and more frail than a normal child of his age. The skin and mucous membranes showed a decided pallor. Although the adenoids had been removed twice, the external nares were pinched and the voice nasal in quality. Palpation, however, did not disclose any great excess of adenoid tissue. The tonsils were cleanly removed. No adenopathy existed. The thorax was strikingly barrel shaped, with a little tendency to pigeon breast. At the time of examination the lungs showed distention, but no evidences of bronchitis or bronchospasm. The heart and vessels were negative, as were also the abdomen and extremities.

Routine examination of the urine and blood showed no abnormalities. No eosinophilia was demonstrated. Only moderate enlargement of the bronchial root glands was noted in the roentgenograms of the chest.

Table 2. Treatment Record. Case 2. R.T. Age 8. Diagnosis- Bacterial Asthma.

Date	Dose of Vaccine	No. of Bacteria (millions)	Reaction Local	Reaction Constitutional	Clinical Condition & Remarks.
Mar. 30,1921:	0.1 cc	100	0	0	
April 4,1921:	0.2 cc	200	0	0	
April 11,1921:	0.3 cc	300	0	0	
April 18,1921:	0.3 cc	300	0	0	Has had cold in head following exposure without wheezing.
April 25,1921:	0.4 cc	400	0	0	
May 2,1921:	0.5 cc	500	0	0	
May 9,1921:	0.5 cc	500	Slight:	0	
May 16,1921:	0.5 cc	500	0	0	
May 23,1921:	0.5 cc	500	0	0	
June 1,1921:	0.6 cc	600	0	0	Patient has been exposed to chilling; developed a cold but no asthma.
June 6,1921:	0.6 cc	600	0	0	
June 13,1921:	0.7 cc	700	0	0	
June 20,1921:	0.7 cc	700	0	0	
June 25,1921:	0.7 cc	700	0	0	
June 30,1921:	0.7 cc	700	0	0	
Nov. 10,1921:	-	-	-	-	Asthmatic paroxysm following exposure while swimming; cold in head and bronchitis.
Nov. 17,1921:	0.1 cc	100	0	0	Fresh autogenous vaccine containing non-hemolytic streptococci as the predominating organisms.
Nov. 23,1921:	0.2 cc	200	0	0	
Nov. 29,1921:	0.3 cc	300	0	0	
Dec. 6,1921:	0.3 cc	300	0	0	
Dec. 13,1921:	0.3 cc	300	0	0	
Dec. 21,1921:	0.4 cc	400	0	0	
Dec. 30,1921:	0.5 cc	500	0	0	
Jan. 6,1922:	0.6 cc	600	0	0	
Jan. 13,1922:	0.6 cc	600	0	0	
Jan. 23,1922:	0.6 cc	600	0	0	Has had cold and cough for a week but no asthma.
Jan. 30,1922:	0.6 cc	600	Slight:	0	
June 7,1922:	-	-	-	-	No asthma since last treatment; has sneezing attacks in the early morning and rhinitis; these do not develope into asthma.

No cutaneous hypersensitiveness could be elicited to the common food, animal, plant, and bacterial proteins.

Examinations were made of the deep sputum by smear and culture. No tubercle bacilli were found. The bacterial flora in three different specimens of sputum showed a predominence of non-hemolytic streptococci with some colonies of staphylo-

cocci and Micrococcus catarrhalis. A vaccine was made containing the mixed organisms in a dilution of 1,000,000,000 to the cubic centimeter. This vaccine was administered in the dosage and at the intervals given in the treatment record (Table 2).

Summary and Clinical Course.—The factor of infection of the respiratory tract in this patient was very striking: repeated head colds at the age of three, whooping-cough at four, and influenza and bronchopneumonia at six years of age. Marked relief from asthma followed the two courses of vaccination, one course lasting about three months and the other two months. Following immunization the first time the patient remained free of seizures for seven months, and then had a recurrence after exposure to chilling. Now, four months after the second course of vaccination, the patient is still free from asthma.

Case III.—The third and last patient whom I shall present is a boy six years of age, first seen in October, 1921. In this instance, also, the present illness began after the first year of life. Prior to that the child was normal in every particular: born at term, growth and development continued normally. Bottle feedings were supplemented before the end of the first year with bread and one egg daily. No idiosyncrasy to any food was noted except for the development of hives, more latterly following the ingestion of acid fruits. When a year old the patient had a severe attack of bronchopneumonia lasting six weeks. Soon after recovery from this illness the child had his first wheezing spell. After this the spells recurred at intervals of about three weeks. A change to the warmer climate of Sonoma, California, brought about great relief, for, during a year there, the patient had only one severe paroxysm. The bronchitis and cough, however, continued unabated in a mild form. At the age of three he passed through an attack of whooping-cough. Although free from asthma during this illness, the paroxysms returned with increased severity and frequency following the whooping-cough. The spells now came

on at intervals of two weeks to two months, the latter period being the longest free interval. Another attempt was made to obtain relief by changing to a warmer climate, but this time without relief. Removal of the tonsils and adenoids did little good so far as the asthmatic attacks were concerned.

The individual attacks last from three to seven days, and each is characterized by marked inspiratory dyspnea, cyanosis, and struggling. With a loosening up of the mucus in the bronchial tubes the spell begins to abate. Cold winds, overexertion, overloading the stomach, and constipation serve as predisposing causes. No relationship has been found to exist between the attacks and exposure to food, animal, or plant protein.

On examination, the child was found to be very well developed for his age, and of good nutrition. Weight, 53 pounds. The mucous membranes were of excellent color. A slight obstruction to free breathing was noted in the left nasal passage. Tonsils and adenoids had been cleanly removed. No infection existed in the teeth. A slight general glandular enlargement was present. The thorax was well formed and the anteroposterior diameter not greater than would be expected in a child of the patient's age. Both lungs were a little distended, but of good expansion. The breathing was puerile, and at the time of examination no râles were audible. In every other particular the physical examination was negative.

Roentgenograms of the chest showed only a moderate increase in the markings of the bronchial root glands.

Cutaneous protein sensitization tests, carried out with a large number of the common food, animal, plant, and bacterial proteins, were negative, save for a slight reaction to Streptococcus hemolyticus. Repeated examination of the sputum for tubercle bacilli gave negative results, and several cultures of the deep sputum showed a constant bacterial flora: Streptococcus non-hemolyticus, chiefly viridans, with some colonies of a hemolytic streptococcus. The vaccine prepared contained these organisms in a dilution of 1,000,000,000 to the cubic centimeter. The dosage and the intervals between injections are given in the treatment record (Table 3).

Table 3. Treatment Record. Case 3. E.S. Age 6. Diagnosis- Bacterial Asthma.

Date	Dose of Vaccine	No. of Bacteria (millions)	Reaction: Local	Reaction: Constitutional	Clinical Condition & Remarks.
Oct. 21,1921:	0.1 cc:	100	0	0	
Oct. 26,1921:	0.1 cc:	100	0	0	Slight cold in head; running from nose; no wheezing.
Oct. 31,1921:	0.1 cc:	100	0	0	Has had spell of wheezing beginning after last injection and lasting two days; much expectoration.
Nov. 7,1921:	0.1 cc:	100	0	0	Well.
Nov. 14,1921:	0.2 cc:	200	Slight redness:	0	Excellent week.
Nov. 21,1921:	0.2 cc:	200	0	0	Good week; no wheezing; appetite fine.
Dec. 5, 1921:	0.3 cc:	300	0	0	A little tightness in chest on exertion; slight catarrhal condition of nose.
Dec. 12,1921:	0.3 cc:	300	0	0	Tightness in chest;no wheezing.
Dec. 23,1921:	0.3 cc:	300	0	0	
Dec. 30,1921:	0.4 cc:	400	0	0	A short wheezing spell during past week, following a cold in head; easily relieved.
Jan. 9,1922:	0.4 cc:	400	0	0	Slight paroxysm 4 days ago lasting only one-half hour.
Jan. 16,1922:	0.5 cc:	500	0	0	
Jan. 23,1922:	0.5 cc:	500	0	0	
Jan. 31,1922:	0.6 cc:	600	0	0	
Feb. 13,1922:	0.4 cc:	400	0	0	Has just passed through a spell of influenza. Fever up to 103 degrees F; cough and expectoration but no wheezing.
Feb. 20,1922:	0.5 cc:	500	0	0	Condition excellent.
Feb. 28,1922:	0.6 cc:	600	0	0	Condition excellent.
Mch. 6,1922:	0.7 cc:	700	0	0	Condition excellent.
Mch. 14,1922:	0.5 cc:	500	0	0	Slight wheezing spell during week; followed chilling; accompanied by fever, rhinitis and gastro-intestinal upset; duration only several hours.
Mch. 21,1922:	0.5 cc:	500	0	0	Condition excellent.
Mch. 28,1922:	0.6 cc:	600	0	0	Condition excellent.
Apr. 3,1922:	0.6 cc:	600	0	0	Discharged.

Summary and Clinical Course.—In this patient, as in the two former ones, a respiratory infection immediately preceded the onset of the asthma. First, bronchopneumonia and later whooping-cough so lowered the resistance of the bronchial mucous membranes that they became the fertile soil for a chronic infection. A course of immunization with an autogenous vaccine carried on over a period of about five months has brought great relief to this patient while the treatment was being given. At the present time, some six months since the last vaccine treatment, the child still continues free of asthma. Only on two occasions during this period was he threatened with asthma. In each instance the attack was abortive, lasting less than two days, and accompanied only by a watery discharge from the nose with some tightness in the chest, but without wheezing.

Relation of Infection to Asthma.—Now I wish to emphasize certain points brought out by the clinical course of these 3 children and to discuss briefly our present viewpoints concerning the form of asthma under consideration.

The carefully taken histories of these children, as well as those of the greater number of adults, whom we have studied and treated for asthma, show over and over again the following facts: first, the attack of asthma started after some respiratory infection, whooping-cough, influenza, bronchopneumonia, grip, a neglected bronchitis, or a tonsillitis; second, every subsequent attack, or series of attacks, was introduced by a new cold or bronchitis, coming on, as a rule, at a time of year when nasobronchial infections are prevalent; third, a large number of asthmatics are the subjects of chronic bronchitis from which they suffer more or less even in the intervals between attacks. This bronchitis, whether it can be shown to have antedated the first asthmatic paroxysm or whether it is a concomitant affair of subordinate nature, developing secondarily to the asthma, should be looked upon as the inciting cause of the recurring attack.

Those who have given particular time to the study of this disease are more or less in accord that asthma is a symptom-complex caused by a foreign protein, which produces its effect by gaining entry into the body from without, or by absorption from some focus, usually of bacterial growth within the body. Now, it is fair to say that not all agree with the view that bacterial infection is a true etiologic factor giving rise to hypersensitiveness in the sense in which the term is used today, but nearly all are agreed that secondary infection, notably of a congested and edematous bronchial mucous membrane, may serve to bring on and to perpetuate asthmatic paroxysms, the original cause or causes of which may have escaped detection. It is not unlikely that the careful observations of Cooke and of Vander Veer, of New York, on the sensitiveness of some asthmatic patients to the extracts of certain organic dusts in their surroundings, may help to reduce the number of instances now attributed to bacterial hypersensitiveness or to bacterial infection.

However that may be, the fact remains that many observers have attained good results in a large percentage of patients, either by the eradication of a focus of infection surgically where possible, or by the use of bacterial vaccines made from the same strains of bacteria which are causing the infection, or most preferably where indicated by surgery and vaccination combined. Where chronic infection of the bronchi has been found responsible for the asthma, autogenous sputum vaccines, properly administered in gradually increasing doses over a sufficiently long period of time, have given very encouraging results in the hands of a number of clinicians. Montgomery and Sicard in 1917 isolated streptococci, either hemolytic or non-hemolytic, from each sputum, and reported satisfactory results by vaccination in all but 2 of 16 patients. In 1919 Walker, of Boston, obtained relief from asthma in 75 per cent. of patients who were found sensitive to bacterial proteins, and in a non-sensitive group relief in 40 per cent. and marked improvement in 25 per cent. of the patients. Later, in 1920, Rackermann, working at the Massachusetts General Hospital, published the results of his observations on 39 patients, and concluded that the treatment was successful in fairly close accordance with the presence of a positive skin reaction to the intradermal injection of the pure autogenous vaccine. On the other hand, one should not overlook the conclusions of Vander Veer, of New York, who, in a paper published in July of this year, states that his results with bacterial vaccines have been very unsatisfactory.

Relation of Sputum Bacteria to Asthma.—In isolating the predominating organisms from the sputum obtained from the deep respiratory passages, and in the preparation of vaccines from them, we have followed, with minor modifications, the technic used by the Boston workers. A suitable nugget of sputum is obtained in a sterile sputum bottle, and washed about three times in sterile salt solution. A smear from such a specimen is then made on a blood-agar plate. Colonies from this plate are then streaked on a second blood-agar plate, and then on a third, to insure purity. From these several colonies of each

type of organism are transferred to slants of Löffler's medium so as to insure sufficient growth. After twenty-four hours tests for purity are made, and then each slant is washed off with the water of condensation and about ½ c.c. of this is transferred to a tube of Avery blood-broth. For streptococci, the reaction of this medium should be about P_H 7.8. The twenty-four-hour growth in broth is then washed three times in saline, the last washing being carried out in the Hopkins graduated tube. A mixed suspension is then made of the various types of organisms, approximating their predominence on the blood-plates. The bacteria are killed by heat at 60° C. for one hour and tested for sterility. The vaccines thus made were diluted so that each cubic centimeter contained 1,000,000,000 bacteria.

Approximately 120 sputum cultures were made on the sputum of over 50 patients, and about 247 organisms were isolated in this way. For purposes of emphasizing the relative frequency with which the various bacteria occur I have listed them in the following table in the order of their prevalence:

Table 4. The Percentage of the Various Types of Bacteria occurring in the sputum of Asthmatic Patients.

No. of each Organism.	Organism	Per cent.
81	Non-hemolytic streptococci	33
35	Hemolytic streptococci	18
44	Micrococcus catarrhalis	13
29	Staphylococci	12
22	Pneumococci	9
23	Gram-positive diplococci	47
10	Diplostreptococci	
1	Gram-positive bacillus	
1	Gram-negative bacillus	others....15.
1	Bacillus of Friedlander	

I wish to call your attention to the great preponderance of streptococci, both non-hemolytic and hemolytic, in the deep respiratory passages of these patients. No doubt the percentage

would have been even higher if, in our earlier work, we had studied more carefully the cultural characteristics of the Gram-positive diplococci and diplostreptococci, which I have placed in a miscellaneous group. Pneumococci and Micrococcus catarrhalis have been found much less frequently of late because we have become more successful in carefully obtaining and in washing our sputum specimens. These organisms are probably only infrequently responsible for this type of asthma. For the most part our observations are in agreement with those of Rackemann, who, in a study of 129 organisms derived by culturing the sputum of asthmatic patients, found streptococci in nearly 75 per cent. of the cases.

Autogenous Vaccines in Bacterial Asthma.—The treatment records of the patients presented give the dosage and the time interval between injections of the vaccine. In most instances we began with small doses of pure vaccine given at seven-day intervals, each succeeding dose, being regulated according to the reaction of the patient to the previous dose. The initial dose varied from 50,000,000 to 100,000,000 organisms, and the final dose amounted to anywhere from 500 to 1,000,000,000 bacteria.

Only a very small percentage of our patients gave a positive skin test to any bacterial protein, but a slightly larger number showed a fairly well-marked local reaction at the site of inoculation. We are not convinced from our experience that a successful therapeutic result is in any way directly related to the presence of a positive skin test to a bacterial protein or to the occurrence of a local reaction, since the greater number of patients who showed neither response were definitely improved both subjectively and objectively as a result of vaccine treatment. A considerable number of our patients have been free from paroxysms for a little over a year, and many have had relapses necessitating revaccination. Our experience is as yet too small and the time elapsing since the last period of immunization too short to justify any definite statistics as to the percentage of our successes. Whereas it is not permissable to use the term *cure* in connection with so baffling a disease as asthma, I have

come to feel that we are justified in employing the terms *improved* when the interval between attacks as well as the duration of each paroxysm has been shortened, and *relieved* when a patient, who had been having frequent attacks of asthma, after vaccination goes for six months, a year, or longer without an attack. The majority of our patients have been *improved* or *relieved* in this sense.

For those treated persistently enough, who did not show improvement or relief, a number of possible explanations suggest themselves: first, the bacteria isolated may not have been the cause either wholly or partially; second, they may have been only partly the cause, improvement being dependent upon some other undiscovered factors; third, the offending bacteria may have been of types not readily producing immune reactions; fourth, irreparable damage may have resulted in the bronchi and lungs due to the long-standing bacterial invasion. Doubtless the last two factors help to explain the more successful results obtained by vaccination in children having bacterial asthma. In them we have seldom encountered the grade of chronic bronchitis and pulmonary fibrosis so frequent in adult asthmatics; and in them vaccination is more likely to evoke a resistance to the invading organisms.

CONTRIBUTION BY DR. LEROY H. BRIGGS

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FEVER OF LONG DURATION

ANY fever, more or less continuous, which persists for longer than a few days becomes a definite problem, frequently beset with the greatest diagnostic difficulties. Embarrassing as it is for a case in the hospital wards, surrounded by every modern aid, to go for days with the cause unknown, it becomes doubly so in private practice. It is, indeed, the unusual layman who will remain charitable toward us in our often futile efforts to ascertain the source of the persistent fever; and we daily sink in comparison with the doctor of a generation ago who rarely was at a loss to name the disease "gastric fever," "mountain fever," or what not, unfettered by the bonds of modern scientific knowledge. Only in the faith of thorough work well done are we secure, in our own minds at least, in the realization that the impossible cannot be accomplished and that time eventually will solve the riddle. The recent occurrence in the writer's experience of several fevers of this type, together with the incidence of some unusual temperature courses in known conditions, has prompted the thought that a brief review of the subject would be timely.

By far the commonest cause of a continued pyrexia is one of the infections, bacterial, protozoal, or mycotic, and a sound knowledge of these parasites—medical, bacteriologic, and geographic—is essential. Even within the confines of the United States a number of infectious diseases are closely limited to certain localities, a recognition of which would put the wise clinician on guard at once for what might otherwise prove a baffling affair. To mention some of our own geographic diseases,

we may include Malta fever, Rocky Mountain spotted fever, coccidioides, and the more recently discovered tularemia. Malaria in a measure depends on physical geography, but the parasite may be harbored so long in a latent form that it must be thought of as a ubiquitous disease. The fevers of other than infectious origin are greatly in the minority, being largely limited to neoplastic and blood conditions.

Of the bacterial infections, the typhoid and tubercle bacilli, together with the pyogenic cocci, will account for the vast majority. Typhoid and the paratyphoids, thanks to prophylaxis and efficient health boards, are fast becoming very infrequent diseases. Up to ten years ago it was proverbial that a patient with a continued fever and nothing to account for it should be considered as having typhoid until proved innocent, and such a dictum was more often right than wrong. The accurate early diagnosis is far from simple. Where one has access to a laboratory, blood-cultures during the first few days of fever will often settle the question absolutely, and, where possible, never should be neglected. Simple white and differential counts, a procedure well within the capabilities of anyone who aspires to practice medicine at all, frequently furnish the convincing evidence of a leukopenia and relative lymphocytosis to be added to the general appearance, splenomegaly, and rash, or will rule it out by a frank leukocytosis. It is to be regretted that the advent of the numerous "clinical laboratories" seem to make it beneath the dignity of the physician to do blood-counts, and, in consequence, the patient is burdened with the necessity of considerable added expense, or, what is more usual, no decent investigation at all. One cannot place as much reliance on the Widal reaction as formerly owing to the prevalence of the use of typhoid vaccine as a prophylactic or in the shape of foreign protein therapy. Usually the fever, once started, does not reach normal until defervescence occurs, and it has long been stated as a rule that a fever which reaches normal after the first week cannot be typhoid. In this connection the chart shown in Fig. 67 is of interest. The patient, a boy of twenty-one, entered the ward on the sixth day of

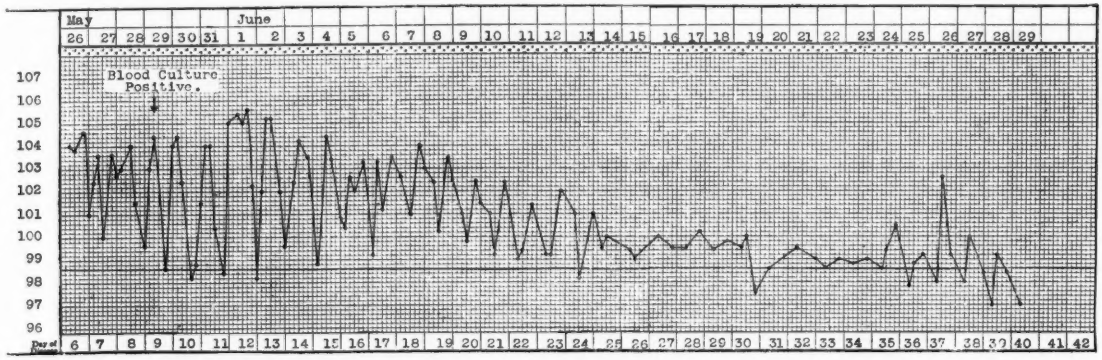

May
June
26 27 28 29 30 31 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Blood Culture Positive.
107
106
105
104
103
102
101
100
99
98
97
96
Days of Disease
6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42

Fig. 67.

illness. The only findings on repeated examinations were a slight splenic enlargement and some questionable rose-spots. Typhoid was considered most unlikely on account of the type of temperature, but the demonstration of the bacillus in the blood, with later a positive Widal, and the further course, left no doubt, although the fever did not approach the usual picture until the third week.

Probably the commonest cause of prolonged fever is the tubercle bacillus. In most cases the physical findings leave no question as to the etiology, and, fortunately, the instances of miliary tuberculosis with high fever and little to show for it are rare. Here a rapid pulse and respiratory rate, with cyanosis out of proportion to what is in the lungs, are the most suggestive signs. Blood-counts are of little help, although the leukocytes as well as the percentage of neutrophils are apt to be higher than in typhoid. Root-gland tuberculosis undoubtedly is to blame for many of the unexplained fevers in adolescence, but their presence can rarely be proved unless the complement-fixation test holds something in store for the future.

Infection by pyogenic streptococci and staphylococci makes up the third great class of bacterial disease characterized by long-continued febrile disturbance. They can be discussed under two heads—septicemia and local foci—and both at times may be decidedly puzzling. Due to the writings of Osler, Horder, Libman, and others the picture of a subacute septicemia caused by the streptococcus is now well recognized. A long-continued fever of low grade, peculiar earthy, yellow color, enlarged spleen, emboli in skin, kidneys or retinæ, with the renewed activity of an old heart lesion, are almost pathognomonic of a streptococcemia with a focus on the heart valves. Lewis has emphasized recently the frequency of clubbed fingers as a sign of such sepsis. The frequently remarked fact that this disease seems to be increasing probably has its explanation in the more general recognition of the condition rather than in any increased prevalence.

The fulminant type of septicemia and pyemia following septic abortion, sinus thrombosis, infected wounds, or osteo-

myelitis hardly ever gives diagnostic difficulty, although at times the site of origin may be in doubt. In this regard an experience upon which the writer always looks back with chagrin may be quoted. A man entered the hospital with a very evident pyemia obviously connected with a thrombosis of the femoral vein, and died in a few days. Owing to his desperate condition and the self-evident disease a digital examination of the rectum was omitted, and consequently the pathologist later enjoyed the demonstration of the true origin of the trouble as a periprostatic abscess connected with a vein. Blood-cultures, of course, offer the final proof, but negative results should be discounted in the face of strong clinical evidence to the contrary. As has often been said, one's percentage of positives depends largely upon the skill and interest of the laboratory staff.

Local foci of infection with pus collections are common offenders, although no brief is held for the small tooth abscess or infected tonsil. These two focal infections may give rise to definite lesions in joints or kidney, but rarely in my experience are they the source of a long-continued fever except as a possible port of entry. Perinephritic abscess is notoriously latent and its possible connection with previous furunculosis should always be remembered. The presence of a localized edema of the tissues of the back may be the first hint of its existence. Abscesses in liver or brain fortunately are infrequent, but nevertheless real and well hidden. The overemphasis of amebic lesions of the liver has done much to make the present generation forget that any infection in the field of the portal circulation may give rise to a metastatic liver abscess, and bronchiectasis as a forerunner of brain abscess is well known, but often forgotten.

The streptococcic infections of the lung and pleura of the past five years have written new chapters in the physical diagnosis of the chest as well as added to our diagnostic burdens. A central streptococcic pneumonia may give rise to a week or ten days of fever before it approaches near enough to the surface to be definitely recognized. Cautious needling of suspicious areas always is justified in the search for wall-off empyemas

as a factor in keeping up a pyrexia after such a respiratory infection. A large abscess in the peritoneal cavity would seem easy of discovery, but the experience of having such a one under observation in a hospital for a month with an exploratory, fruitless except for the finding of extensive adhesions, and the later discovery at autopsy of a large postperitoneal collection of pus from a ruptured duodenal ulcer, has been the lot of the writer, a circumstance highly conducive to humility. Pyelitis without pain is more frequent than supposed, especially in childhood, and overlooked more often than it should be. In a man seen recently the original infection of five years before was called "typhoid" until a urine examination disclosed the true cause. Even after this the persistence of an afternoon rise in temperature was considered tuberculous until the removal of a badly infected non-tuberculous kidney cleared up the whole picture. The few examples mentioned are only some of the sites where pyogenic infections may lurk and pus collect awaiting drainage. Our only means of success in these at times most obscure fevers is by exhausting every avenue of search for the offending focus. As contrasted with typhoid and tuberculosis they usually are characterized by a leukocytosis, and the temperature course is more apt to be of the irregular septic type.

The rheumatic fever complex, although usually becoming rapidly afebrile under treatment, at times may give rise to a persistent pyrexia. The term "rheumatic fever complex" is used advisedly to cover the arthritis, carditis, chorea group of cases, found most often in children, usually associated with diseased tonsils, and responding more or less satisfactorily to salicylate therapy. Diagnosis rarely is in doubt, yet sometimes one may question as to whether he is dealing with a case of acute rheumatic fever or a multiple infectious arthritis, and the development later in the course of a cardiac lesion may be the only means of settling the matter. Although it is still an open question whether this is a bacterial disease, it is mentioned here because of its close clinical connection with the other streptococcus infections.

That the meningococcus at times may give rise to a septi-

cemia has been known for years through the reporting of isolated cases, but the work of Herrick in the army brought the whole question of meningococcic sepsis before the medical public in a striking way. He has shown that this organism may invade the blood-stream without meningeal involvement, with the clinical features of an acute fulminant disease with extensive purpura, or as a subacute sepsis with irregular fever, joint pains, and erythematous or purpuric rashes. In the latter group belongs the patient whose temperature chart is shown in Fig. 68. She was a woman who was in a hospital several months with recurrent febrile attacks associated with joint pains and a diffuse erythematous rash, but comparatively free from symptoms in the afebrile periods. After several negative results a meningococcus was grown from the blood on two separate occasions. The spinal fluid was negative and there were no meningeal symptoms at any time. She was being given antimeningococcus serum intravenously, with improvement, when she met with an accident resulting in a severe head injury from which she died in three days. Autopsy revealed a large recent subdural hemorrhage as the immediate cause of death, together with small multiple foci of infection scattered through heart muscle, spleen, liver, and kidneys.

Malta fever, running a course similar to typhoid, but with the more constant occurrence of relapses, is of interest because it has been found endemic in Texas. The disease is transmitted through the medium of goat's milk and the recent fad for drinking this, together with the increase in goat herds throughout the country, may bring about its more wide-spread distribution. Caused by the Micrococcus melitensis, diagnosis rests upon the results of blood-cultures and in the agglutination reaction with this coccus.

Another animal-borne disease of man, recently described by Francis, of the Public Health Service, is the infection by the Bacterium tularense. Probably transmitted from the rodent to the human by the bite of an insect, it is characterized by a high fever of a continuous type of several weeks' duration, together with an adenitis, often suppurative, regional to the

bite. Nearly all the human cases other than laboratory infections have thus far been confined to Utah, although the organism was found first in the ground squirrels in Tulare County, California. A third focus was described in Indiana. As in Malta fever, the final diagnosis rests on the agglutination reaction, although the occurrence of a continued fever with a local suppurative adenitis in a farm worker or in one who has come in contact with squirrels or rabbits should lead to the suspicion of tularemia.

Glanders or farcy, a very rare infection in man, gives rise to a continuously high fever. Diagnosis is difficult, but a history of handling horses, together with adenopathy, skin and mucous membrane lesions, is suggestive. As the disease is a septicemia the causal organism, Bacillus mallei, may be grown in blood-culture.

Of the infections caused by protozoa and other animal parasites and manifested by pyrexia of long duration, malaria, of course, is pre-eminent. Malaria, in this country at least, is one of the most satisfactory of infectious diseases to encounter, since its cause usually can be determined readily and speedily, and an efficient treatment started with, as a rule, rapid results. Osler's very true statement that "any fever which resists quinin is not malaria" unfortunately has been the cause of the neglect of proper blood examinations before treatment and, consequently, most fevers arising in malarial districts are given quinin without proper investigation. This naturally leads to mistakes at times, and I have always insisted that plasmodia be found before treatment be started, in the belief that the febrile case of malaria is rare in which parasites cannot be discovered by the competent observer within forty-eight hours. A man labeled dengue fever during his four months' residence in the Malay Peninsula was given quinin occasionally for his continuous low fever and malaise, although no blood examinations were made. Estivo-autumnal parasites promptly were found on his return to this country and the whole condition immediately cleared up under intensive quinin therapy. From experiences such as these one is tempted to add to Osler's

axiom the admonition "no quinin in fevers without plasmodia in the blood."

Trichiniasis in the milder cases often resembles typhoid in regard to the fever, diarrhea, prostration, and rose-spots, but the differential blood-count is so absolutely diagnostic between the two that there can be no excuse for confusing them together. The classical picture of the edematous face and severe muscle pains may not be seen in the light infections, and the disease no doubt is overlooked simply because no differential counts are done during the course of the fever.

Spirochetal disease, one of the most important in all medicine, naturally plays a prominent part as a fever producer, and no discussion could be complete without the mention of syphilis. In the secondary stage fever occurs frequently, but as a symptom rarely dominates the picture. In late visceral lues, however, a continuous fever lasting for months has long been known, and may mimic typhoid, tuberculosis, or sepsis. The liver undoubtedly is the organ most commonly involved in febrile syphilis and is frequently accompanied by a splenomegaly or an anemia. In the well-known case of Edwards a septic fever persisting for two months with daily variations at times of as much as 8 degrees subsided almost within a week from the beginning of specific treatment. In these days of routine Wassermann tests in hospital and clinic work such an instance would be rare, but in private practice it still occurs. Our most frequent blunder seems to be in thinking that the social status of our own particular patient is such that it precludes syphilis.

Among other febrile spirochetoses are rat-bite fever, infectious jaundice, and spirochetal bronchitis. Considered rare, they are assuming more importance in this country and must be reckoned with. True relapsing fever, found occasionally as an importation in a seaport town, has twice been reported endemic in this country, and probably will be found more widespread. Without blood examination it readily would be mistaken for malaria, the natural drop in fever at the end of a paroxysm being taken for the quinin effect when that drug is given blindly. Vincent's stomatitis and angina gives rise to a con-

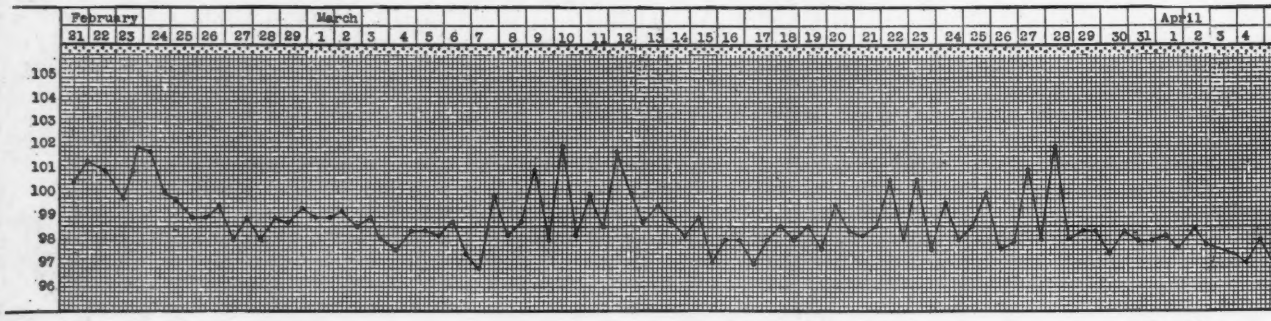
tinuous fever of low degree, but the local signs are such as to direct attention immediately to the source.

Rocky Mountain spotted fever, limited to the northwestern states, and especially Idaho, Montana, and Wyoming, occurring in the spring and early summer, transmitted by a tick to man and probably caused by a micro-organism of varying morphology, presents in the infected districts a frequent cause of temperature elevation for from two to three weeks. The diagnosis is made from the characteristic macular and purpuric rash, appearing first on wrists and ankles and later on other parts of the body. The seasonal and geographic incidence of the disease likewise is of the greatest importance in its identification. Typhus fever, probably akin to this but with a rash of somewhat different character and distribution, would be difficult of differentiation were it not for the fact that the one is a disease of open mountainous country, while the other is a disease of filth and overcrowding in cities.

Fortunately the rarity of mycotic disease saves us from more numerous errors in diagnosis. In the United States there are several varieties of these closely related fungous infections, and as they most often resemble tuberculosis, cases are found occasionally in hospitals devoted to that condition. Actinomycosis in the classical form of "lumpy jaw" is recognized readily, but when it affects only the lung it is infinitely more difficult of recognition. These infections if limited to small skin lesions do not necessarily give a pyrexia, but when visceral or systemic involvement is present then a fever occurs which may continue for months. Diagnosis can be made only by culturing and identifying the particular fungus present. Two varieties are of especial interest inasmuch as they are fairly well limited to certain localities—the blastomycoses of the territory around Chicago and the coccidioides of the San Joaquin Valley in this state.

NON-INFECTIOUS CONDITIONS

Of the non-infectious conditions responsible for a long-drawn-out fever malignancy certainly occupies first place.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April
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Fig. 68.

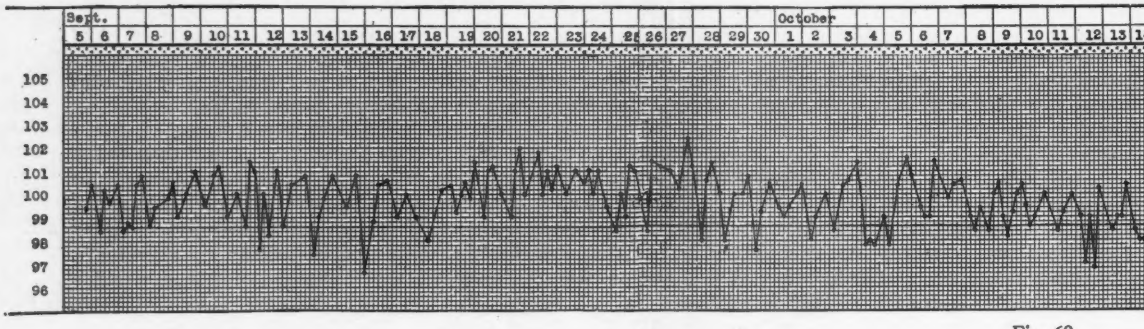
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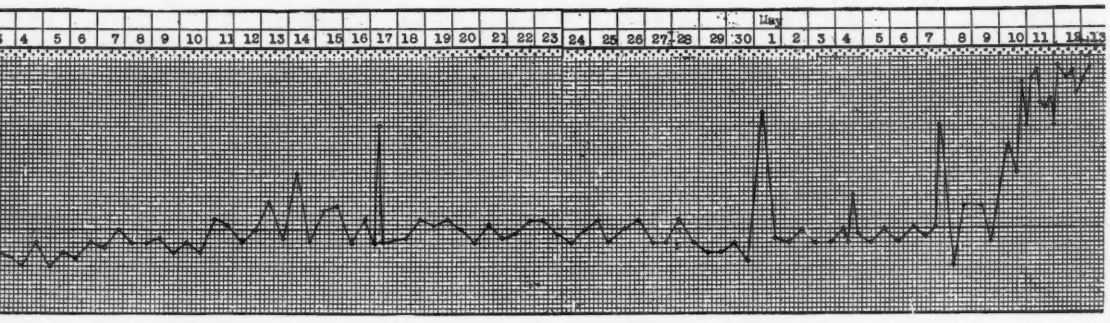
Fig. 69.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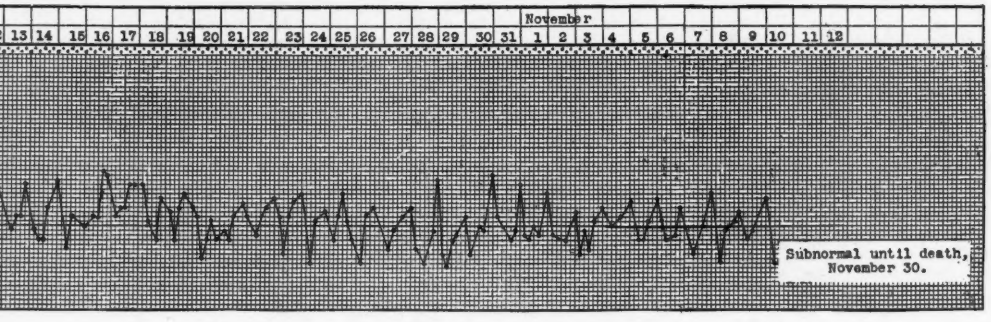
November
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 1 2 3 4 5 6 7 8 9 10 11 12
Subnormal until death, November 30.

Here an intermittant type of fever probably is more characteristic than a true continuous one, although from statistics, especially of digestive tract carcinoma, the latter seems by no means uncommon. A study of the question is being made in this clinic and, although as yet incomplete, results so far would indicate that while occasional rises are common, a continuous fever lasting weeks or months is infrequent and then usually due to ulceration. In Fig. 69 is shown the fever curve of a man who entered the ward in fair condition, but with a definite stomach carcinoma. No cause other than this could be found for his prolonged fever, a fact confirmed later at postmortem. Lymphosarcoma and Hodgkin's disease, conditions in a measure allied to malignancy, are almost constantly accompanied by pyrexia. Frequently this takes on a highly characteristic picture, the so-called Pel-Ebstein fever, marked by fever for some days, alternating with periods of normal temperature, the whole cycle recurring over long periods of time.

A type of fever not unlike this last is that seen in the condition known as "ball-valve calculus," where a gall-stone is impacted at the end of the common duct and periodically blocks the flow of bile. During the interval of obstruction there is jaundice together with a febrile reaction, these subsiding as the stone sinks back and the obstruction is relieved. This alternating pyrexia, known as the "intermittent hepatic fever of Charcot," may continue for months and greatly resemble that of the Pel-Ebstein type.

Disease of the hematopoietic organs, notably the leukemias and pernicious anemia, usually are marked by an irregular but continuous fever. In pernicious anemia this may at times give rise to diagnostic difficulties on account of the similarity of the picture to subacute bacterial endocarditis, with its fever, anemia, pigmentation, splenomegaly, and heart murmurs.

In the at present well-tilled field of the endocrins fever does not play a prominent part. Overactivity of the thyroid, probably in consequence of the speeding up of metabolism, may give rises in temperature over a considerable period. The fruste form of hyperthyroidism, with its loss of weight, rapid

pulse, nervousness, and low-grade fever, formerly frequently was mistaken for early tuberculosis until the advent of basal metabolic determinations made the differentiation easy.

Of diseases of the nervous system, epidemic encephalitis, like poliomyelitis, is ushered in by a fever of no definite type. Usually of too short duration to be considered with the continuous fevers, it may sometimes persist for a time as a major symptom. In one man the only symptoms for three weeks were fever ranging from 99° to 102° F., indefinite muscle pains, and diminution of the deep reflexes, until paralyses of arm, tongue and eye muscles, parasthesias, and somnolence marked the condition as lethargic encephalitis. Tumors, vascular insults, and traumata of the brain and cord may at times lead to prolonged and erratic elevations in temperature, probably largely due to disturbances of the heat-regulating center. At times this may lead to real difficulty. A woman the victim of a left-sided hemiplegia from a thrombosis, immediately afterward developed a fever, at first of low grade, but later becoming continuously high and remaining so until death two months later, and defying all efforts to ascertain its source. As no postmortem was done it is impossible to say whether this was due to difficulties with the heat-regulating mechanism or to some undetermined infection.

Finally there are the cases, fortunately rare, where fever is present over long periods and associated with marked neurotic tendencies. Only after the most exhaustive search, bearing in mind especially hyperthyroidism, glandular and abdominal tuberculosis, hidden streptococcus infections, and syphilis, have we any right to even consider such a fever as the essential fever of a neurosis. Some years ago a young girl was under observation for months with a daily afternoon rise of about a degree, together with definite neurotic symptoms, although these were not even thought of as a cause for the pyrexia. A diagnosis of genital tuberculosis was made and an exploratory done. Absolutely nothing was found on a most careful search, a normal appendix was removed, and a malposition of the uterus corrected. At the request of her family she was assured

that her trouble had been corrected and, whether *post hoc* or *propter hoc*, her fever promptly stopped and has never returned. Such an instance as this sorely tempts one to a diagnosis of "psychic fever," although "fever of unknown origin" is perhaps a safer and more conservative conclusion.

From this résumé it is obvious that at times the problem may be far from simple. As mentioned, the great majority of cases will fall into the typhoid, tuberculosis, and pyogenic group, but even here difficulties frequently arise. Naturally, much help comes from the laboratory. Where a bacteriologist is available blood-cultures should be taken and repeated often. One positive result is worth several negatives. The white count and examination of smears should be done early and frequently. A mistake often made in this procedure is in looking over the smear with a low-power glass in order to save time. The oil immersion invariably should be used and the red cells examined with the whites, as only in this way can the asexual estivo-autumnal parasites be found. The urine must be looked at microscopically if pus is to be found. Finally, daily physical examinations of the patient must be made, unless his condition prohibits, for a lesion which has been hidden for weeks may become obvious over night.

CLINIC OF DR. HANS LISSER

UNIVERSITY OF CALIFORNIA HOSPITAL

A CASE OF ADULT MYXEDEMA AND ONE OF CHILDHOOD MYXEDEMA

OUR mission is to heal the sick. It is, unfortunately, only too true that many of the recent marvelous and fascinating advances in clinical investigation and laboratory science have resulted in intricate and complex diagnoses for the patient, but in little, if any, treatment. In a considerable percentage of medical conditions the curing of disease is at present impossible. An ambiguous therapy permits at times amelioration of symptoms; possibly postponement of death or arrest of the affliction for some years; but our most valiant efforts are embarrassed by a vague uncertainty. In a fair number of maladies, however, we have the good fortune to be provided with more or less specific remedies which enable us ofttimes to abolish a particular disease altogether or almost accomplish this most desirable end. Bearing in mind, then, our principal mission as physicians—to heal the sick—it would seem incumbent upon us all to be most intimately familiar with every diagnostic and therapeutic phase of those maladies for which we have a cure or very nearly a cure. Experience seems to indicate that the time would not be wasted that might be allotted to a small course in the medical curriculum devoted to the intensive study of these particular conditions. For surely the public have a claim upon us to this degree at least, that we should, with practically no exception, recognize and relieve those suffering from curable lesions. Obviously reference is made to such diseases as diphtheria, malaria, syphilis, acute appendicitis, auricular fibrillation, thyrotoxicosis, and myxedema, to name only a

few of them, where early diagnosis and prompt drug serum or surgical therapy will save life and prevent suffering.

Myxedema stands out conspicuously as a malady remarkably amenable to cure. Hardly another disease can be mentioned wherein such truly miraculous changes may be produced through the knowledge gained by medical investigation. It might be thought that these introductory remarks are quite superfluous if it were not for the fact, of which we apparently need frequent reminder, that these "curable" diseases referred to above are often *not* recognized and the patient *not* relieved. From recent writings this has been shown to pertain in the majority of instances to cases of myxedema. Most of these patients have consulted many physicians before coming to the one who recognizes the proper diagnosis. This seems not only a great misfortune, but a phenomenon rather difficult to understand in view of the remarkable signs and symptoms that myxedema patients exhibit. In fact, a careful history and principally a keen inspection of the patient will almost invariably reveal the diagnosis if the examining physician but have it in mind. However, even for those modern "clinicians" who have been brought up under the atmosphere of elaborate laboratory investigation, the diagnosis is today rendered extremely simple, for we have in the basal metabolic rate determination a valuable and reliable test for this marked grade of thyroid insufficiency. It is now well known that the great majority of patients suffering from myxedema (unless already treated with thyroid extract or thyroxin) will show a metabolic rate of more than 20 per cent. below the theoretic normal. The greater number, indeed, will have rates between 30 and 45 per cent. below normal. Such low readings are very rarely obtained in any other disease. Therefore there is no excuse even for those physicians not gifted in the fine art of careful inspection, for they have in the metabolic rate a diagnosis made for them, as it were.

It therefore seems appropriate to record herewith an instance of adult myxedema. Many photographs of the patient are included which tell the story of his illness, from its onset

through its progressive stages until the diagnosis was finally made, and then the startling changes wrought in that individual by thyroxin. There will also be recorded a case of "childhood" myxedema, the term "childhood" being used after the suggestion of Murray B. Gordon, who has recently published a splendid review of this condition as it exists in North America.

A Case of Adult Myxedema.—*G. C., U. C. H., No. 13,471; O. P. D., No. 80,463, age thirty-eight, single, American.* This patient was first seen on the Medical Service October 27, 1921. At this time it was difficult to obtain a complete history because of the listless, apathetic, dull, sleepy condition of the patient. Many times during the course of interrogations he fell asleep, and the answers came slowly in a monotonous, extraordinarily deep voice. The mental processes were evidently sluggish. Before progressing further it may be appropriately remarked that the patient's attitude as described above should of itself attract the attention of the examining physician to the possibility of myxedema.

The *family history* of our patient is unimportant, there being no similar condition in any of his relatives nor even symptoms of a milder hypothyroidism. There is no goiter in the family. Both his father and mother lived to the age of seventy-two and the patient was one of 16 children, only 5 of whom survived an epidemic of smallpox. He was born in Chicago and lived there until he was about one year of age, then for five years he lived in Kansas, and ever since in northern California. From the age of sixteen to thirty-six he worked as an electrician, but has been unable to do any work for the two years previous to our seeing him. Measles and mumps as a child, "typhoid pneumonia" at the age of twenty-one (ill two weeks), jaundice off and on for two years in 1917, and a neisserian infection at the age of twenty-one comprise the infectious diseases that he had contracted. No accidents had occurred and no operations had been performed.

His complaints on entry were puffiness of the body, drowsiness, fainting spells, dragging feet, and slow speech. The onset

of his illness seemed to bear some relation to the so-called "typhoid pneumonia" in that he first noted some swelling when he was twenty-one years old, two weeks after he had returned to work following the above infection. This swelling lasted only a few weeks. This was seventeen years ago. The puffiness became generalized about two years later, at the age of twenty-three, and the patient thought that it was due to poison from the fumes of copper works where he had been employed for three months, although none of the other workers were so affected. This puffiness has persisted in varying intensity since that time, and for many years has involved the face, lips, and eyes particularly, the trunk, arms, legs, hands, and feet, in other words, pretty much the entire body.

About the same time, namely, fifteen years ago, the patient began to be very drowsy. This lethargic, sleepy state steadily increased, and lately the patient has slept from twelve to fourteen hours at night and often several hours during the day as well. He mentions an instance a year ago when he almost went to sleep while getting off a street-car, and, although he was conscious, he could not seem to move of his own volition and had to be escorted home. He remained in this condition for several days, and after that was in bed most of the time for eight weeks. In recent years he has had numerous dizzy spells, frequently falling on the street or at home without really losing consciousness, and, of course, without any convulsions or incontinence.

About eight years ago the patient's feet began to drag and now he moves about very sluggishly. Speech likewise became heavy, thick and slow, and the intonation of his voice became very deep and low. Also about this time his hair began to fall out, leaving him almost bald, but, curiously enough, it has grown in again on three different occasions, only to fall out worse than before. The hair on his body for the most part disappeared. At present he shaves only twice a week. For many years he noticed that he never perspired and, likewise, that he always felt cold. He felt this so acutely at night that he required much covering and even blankets in immediate

contact with his body. Fortunately, we were able to obtain photographs of the patient at the ages of twenty-one, twenty-five, and thirty-one, and the reader is referred to these, which show the alert, bright, cheerful expression prior to the onset of his illness, the change already well evident four years after his first symptoms were noted, the progressive heaviness, puffiness, and thickness of his face and body in the following years,

Fig. 70.—Case I. Age twenty-one years. Note the bright, alert features, plentiful curly hair, slender, erect figure. This picture was taken before the onset of thyroid deficiency.

Fig. 71.—Case I. Four years later, age twenty-five. First evidence noticed of heaviness of the features and gain of weight.

and finally, the extraordinary picture shown at the age of thirty-eight, when he first came under our observation.

On *examination* one observed a large, heavy-set man, drowsy, hard to arouse, moving slowly and very deliberately, and speaking with a deep rumble to his voice. His weight was 180 pounds. Four years before his weight had been 165 pounds, and prior to the onset of his illness, age twenty-one, it had been 145

pounds. His skin was very cold to the touch, very dry, quite thick and rough, with a little scaling. His complexion was very characteristic of myxedema, namely, the "Christmas-red-apple cheeks" described by the French clinicians. This rather pasty yellow background with brilliant red cheeks is a picture quite different from jaundice, pernicious anemia, or nephritis.

Fig. 72.—Case I. Six years later, age thirty-one. Striking change as compared with Fig. 70. Considerable gain in weight. Face puffy; less hair on head. Expression decidedly dull and apathetic.

Fig. 73.—Case I. Age thirty-eight years. Patient's appearance as first seen by us. Myxedema pronounced.

The rest of the body skin was quite pale and the apparent anemia was confirmed by the blood-count detailed below. The axillary, pubic, and body hair was quite scanty. His head was not entirely bald, but almost so, there remaining a few scattered hairs that had the consistency of wiry bristles, being very dry and coarse. His face was round and the features thick and puffy. The palpebral apertures were narrowed, the

eyelids puffy, the nose thick and broad, lips thick, and tongue large. Hearing was impaired in both ears, suggesting a myxedematous infiltration of the mucous membrane of the eustachian tubes not infrequently found in this condition. The pulse-rate varied between 52 and 64 before medication was instituted. The volume and tension were poor. The extremities were thick and looked edematous, but there was very little pitting on pressure. (It is to be understood that only positive findings are herewith recorded and that the organs not mentioned are to be considered as having been found normal.)

Laboratory findings: Urine normal.

Blood-count: Hemoglobin, 58 per cent.; red blood-cells, 2,608,000; white blood-cells, 4000. Differential count normal. Platelets normal.

Wassermann negative.

Phthalein: First hour, 25 per cent.; second hour, 15 per cent.; total, 40 per cent.

Blood-sugar curve: 0.078, 0.111, 0.129, and 0.113.

x-Rays of hand and skull were negative.

Basal metabolism 45.2 per cent. below theoretic normal.

In addition to the above striking findings it should be mentioned that his temperature was markedly subnormal, namely, 35° C.

The patient remained in the hospital for four months. During this time several electrocardiograms were taken which consistently showed right bundle branch lesion and inverted T waves, justifying the assumption of some myocarditis.

After remaining in the hospital for four months the patient reported to the Ductless Gland Clinic, and has been under regular observation there up to the present writing. His treatment throughout has been purely thyroxin administered by mouth, and the dosage employed together with the basal metabolic readings at varying times during its administration can be followed on the accompanying table. It will be noted that the rate gradually rose until it went as high as 5.1 per cent. above normal. It will be noted that about 1 mg. of thyroxin per day was quite sufficient for the first few months to control

the metabolic rate and to produce the extraordinary changes to be described presently, but that tolerance for this drug seems to have increased, in that at the present time he is taking double this amount without further loss of weight, nervousness, or tachycardia, and it seems that 2 mg. of thyroxin per day is necessary to maintain him in his present condition.

Date.	Basal metabolism.	Temperature.	Pulse.	Weight, pounds.	Thyroxin, daily dose.
On entry....	45.2 per cent. below	35	52	176	
Nov. 2/21..	.....	....	..	...	0.4
Nov. 14/21..	26.3 per cent. below	36.8	64	169	0.8
Nov. 25/21..	.....	37.4	80	...	0.8
Nov. 30/21..	.....	....	..	...	0.4
Dec. 11/21..	8.53 per cent. below	36.6	74	151	
Dec. 13/21..	Fine down noticed coming on head. Edema clearing up	....	..	...	0.8
Jan. 5/22..	13.9 per cent. below	36	70	147	1.0
Jan. 19/22..	9.65 per cent. below	36	60		
Jan. 23/22..	.....	36.6	66	...	1.1
Jan. 30/22..	.....	36	54	...	1.2
Feb. 3/22..	5.1 per cent. plus	37	70	143	0.8
Apr. 6/22..	0.12 per cent. below	....	68	147	3.0
May 26/22..	.....	....	68	150	1.5
June 27/22..	Been working past month	....	60	151	2.0

It hardly seems necessary to present any detailed description of the changes that occurred in this patient under thyroxin because the accompanying photographs speak for themselves. It may be remarked, however, that he has grown a heavy amount of hair on his scalp, which is soft in texture; that his weight has decreased 25 pounds; that his temperature has come up to normal; that his puffiness has entirely disappeared; that his facial expression is so completely changed that one would barely recognize him as the individual who first came to us nine months ago. He is back at work, steadily gaining in strength, his speech is rapid and higher pitched, his attitude alert, bright and cheerful, and his entire appearance and demeanor utterly transformed. He again shaves daily. His appetite is very good. He is no

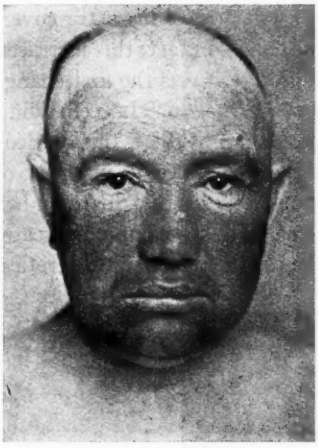

Fig. 74.—Case I. Before treatment was started. Note thick nose, puffy lips, pigmented face, baldness, and sleepy, heavy countenance.

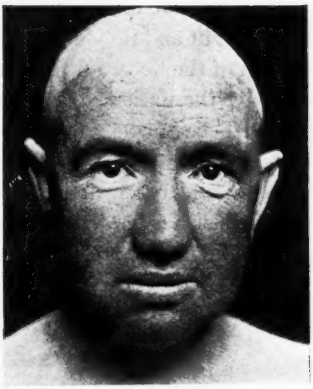

Fig. 75.—Case I. Three weeks after thyroxin was started. Note thinning of chin and neck, and especially the bright, wide-awake expression. Palpebral apertures markedly widened as compared with Fig. 74.

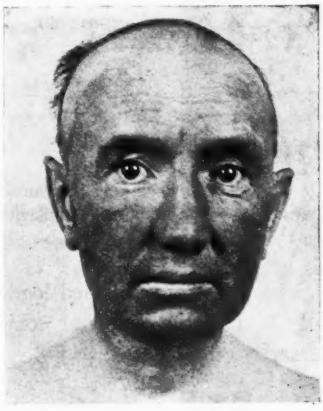

Fig. 76,—Case I. Three weeks later. Note further reduction in puffiness of face and neck. Also note beginning of hair growth, which is of a fine texture. Eyes still brighter.

Fig. 77.—Case I. February, 1922, four months after beginning thyroxin therapy. Note the heavy growth of hair. Facial expression more youthful and cheerful.

longer constipated. He has thrown off most of his extra coverings at night and no longer feels the cold. In fact, this increased warmth of the body and the realization of it was the first change noted by the patient after thyroxin was begun. It seems difficult to believe and embarrassing to record that this patient went the rounds of physicians for over ten years in quest of diagnosis and relief, and it is because of this that his case has been herewith recorded. Myxedema is not a common disease, but it should not be relegated to the category of medical rareties,

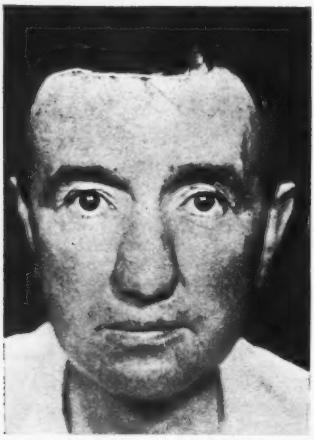

Fig. 78.—Case I. August, 1922, nine months after beginning treatment. Note heavy growth of hair and compare with Fig. 70. One notes a similarity again to picture taken seventeen years ago.

and our experience with that of others recently published leads one to believe that there are many such patients in our communities unrecognized and unnecessarily afflicted.

A Case of Childhood Myxedema.—In Endocrinology, March, 1922, vol. 6, pp. 235–255, Murray B. Gordon presents a study of 280 cases of childhood myxedema that have been reported in North America. Sixty cases had previously been collected and published by Osler. The locations of the 280 cases reported

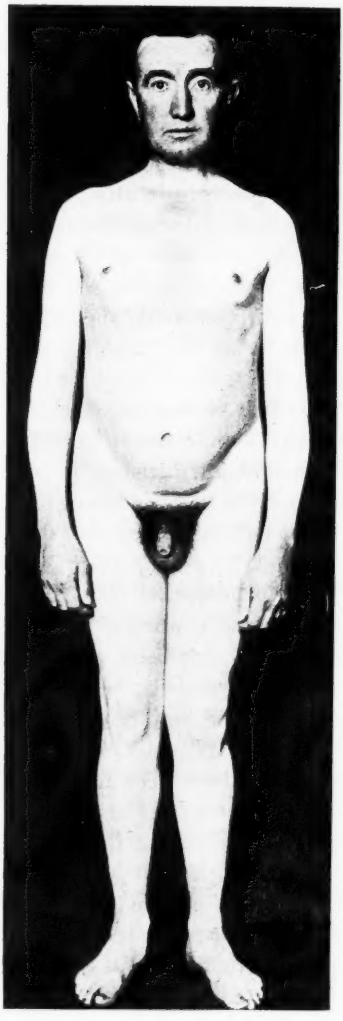

Fig. 79.—Case I. August, 1922. Compare with Fig. 73. Note particularly loss of puffiness in arms and legs, loss of fat from neck and abdomen, and growth of pubic hair.

by Gordon included twenty-seven states and Canada. California receives credit for having reported 4 cases. The case to be recorded below makes the fifth in California. Females have a preponderance over males of 2 to 1 and our patient was a girl. At present clinicians must depend upon the history and physical signs for their diagnosis of childhood myxedema, and this diagnosis is rarely difficult, yet often missed, since it was the feeling of both Osler and Gordon that considerably more than 340 cases have occurred in North America. As yet basal metabolic readings in children seem not sufficiently standardized to be entirely reliable and, therefore, this laboratory aid is not available at the present time. When it is possible to transform a dull, stupid, repulsive looking, idiotic child into a bright, cheerful, normal-appearing youngster by the simple administration of thyroxin or thyroid extract, it seems truly pitiful that such children should be permitted to wander about in their pathetic condition for want of a simple diagnosis and simple therapy, and again for this reason the following case is placed on record.

B. L., U. C. H., No. 9966; O. P. D., No. 73,013, age fourteen, American. The father and mother of the patient, both Americans, appear to be normal, one sister, a year old, seems normal, and one brother, aged twenty-six, is normally developed and of normal intelligence. One brother died of pneumonia at the age of three weeks, and one sister died of spinal meningitis, aged twenty-one. There have been no similar disturbances in the family. There is no history of goiter. The child was born in Humboldt County, California, and lived there for ten years, then in Portland, Oregon, for one year, and since that time she has lived in Corning, California. The mother states that she was "weak and run down" before the birth of the patient, which took place at full term and was a normal delivery. The little girl was breast fed for one year and apparently talked and walked at the normal period. Her teeth came slowly. List of childhood diseases includes measles at three years, whooping-cough at six, mumps at nine, chicken-pox at ten, all without complications. Menstruation began at twelve years. The

periods have been irregular, the second period occurring six months after the first, and since then at intervals of about three months. The flow, however, is then copious, lasting about seven or eight days.

When an infant the patient cried most of the time. When very young she perspired quite freely about the head and face. Possibly the first symptom that has any bearing on her present condition was the fact that from birth on she has always been extremely constipated, often going several days without a stool. When old enough to be understood she began to complain of frontal headaches, which continued until ten years of age, when an operation was performed (to be mentioned presently), since which time the headaches have been less severe. An important point in the mother's story is that the girl's appetite has always been poor, in spite of which she has maintained good weight. The mother has been aware of the fact that the child's skin has always been coarse and dry, thick and rough, and that her hair likewise has been coarse and dry. Vision apparently has always been good and her tongue has never been markedly enlarged, nor has drooling ever been noted.

At about five years of age the mother first noticed a small lump subcutaneously in the midline under the chin and seemingly above the thyroid cartilage. This little mass grew slowly in size for about four years, that is, until the age of nine years, and then increased rapidly to about the size of a walnut. It then hung pendant on her neck and caused the little girl considerable trouble in swallowing. Dr. Rockey, of Portland, removed this growth when the girl was ten years old. According to the mother, only the tumor was removed, and since the operation no change whatever in the child's condition has been noted either for better or for worse except for a decrease in the headaches. The child is irritable at times, sensitive about her condition, and cries easily. Her mental condition when first seen in March, 1921 was about as follows: The mother described her as being interested in things about her, liking to play with dolls, but preferring to be alone and not in the company of other children. Formerly she played with other chil-

dren, but always with those younger than herself. She rarely says much. The mother says that she has been in school in all about thirty-six months at irregular periods, and has recently been placed in the fourth grade.

Examination.—The appearance of the child is very striking. She is heavy set, with thick, dull, stupid features, broad, thick, saddle-nose, puffy eyelids, swollen lips. The skin generally is dry and coarse. The hair grows low on the forehead and is very dry, straight, and coarse. There is a heavy growth between the eyebrows. The shape of the skull resembles that of a monkey. The breasts are unusually well developed and abnormally large for her age. There is a slight growth of pubic hair. The mandible is almost infantile and the lower part of the face is poorly developed. The thyroid gland cannot be felt. The abdomen is enlarged and protuberant. The height of the patient is 4 feet, 6 inches, weight 71 pounds.

Laboratory findings: Urine negative.

Von Pirquet negative.

Wassermann negative.

Blood-count shows a slight secondary anemia. Differential normal.

Plasma carbonates: CO_2 56.7.

Blood chemistry: Urea, 14 mg. per 100 c.c. Non-protein nitrogen 27 mg. per 100 c.c. Creatinin 1.41 mg. per 100 c.c.

Blood-sugar curve: 0.088, 0.135, 0.205, 0.011.

Blood-pressure: 90 systolic.

x-Ray: Chest, negative. Hands, general rarefaction of all bones. Skull, negative except for unerupted canine.

Mental age (Binet-Simon test) seven years—seven years' retardation.

The patient has been under observation in the Ductless Gland Clinic for somewhat over a year, reporting at regular intervals. She has been constantly receiving during this time varying doses of thyroid extract. In one year and a quarter she has grown 1 inch, and during the last few months she has gained 25 pounds. This has been reduced to 7 pounds. Her mental age has not improved under treatment, although she

seems more alert. However, there has been an extraordinary change in her physical appearance, especially in that of her face. This is readily seen by comparing the photographs of her condition prior to treatment with that after thyroid extract had been administered for several months. Her skin has altered remarkably, now being smooth, delicate, and warm. Her hair has likewise been transformed, being luxuriant, glossy, and curly. Her nose is no longer broad, thick, and saddle shaped, and the thick, protruding lips have altered considerably. In fact, one would hardly believe that the child seen in Fig. 80 is the same individual shown in Fig. 81. She is no longer constipated and her appetite has improved. She again plays with other children.

The dose of thyroid extract has varied from 2 grains of Burroughs and Wellcome's tablets daily to 7½ grains. This is not a large dose. For many months she has been receiving 3 grains daily, and any increase over this amount makes her nervous and produces insomnia. After she had been under treatment for about six months pituitary extract was added to the therapy because of the fact that her menstruation was still occurring at intervals of three months. At first she was given anterior lobe pituitary, B. and W., 6 grains daily, and after six months this was changed to whole gland pituitary, 6 grains daily. The effect on menstruation was prompt and satisfactory, periods occurring regularly every month.

The results of therapy in this patient have been very gratifying in some particulars as evidenced by the accompanying photographs. However, there have been disappointments as well, in that her skeletal growth has been slight and her mental advancement, as gaged by Binet-Simon tests, practically nil. Whether better results would have been achieved if the diagnosis had been made many years before is a pertinent inquiry. It might be interesting to change from thyroid extract to thyroxin and note whether additional success is obtained from such a procedure. In any case, specific organic therapy in childhood myxedema is one of the triumphs of medicine. Many cases are entirely cured, others much improved, as in the present

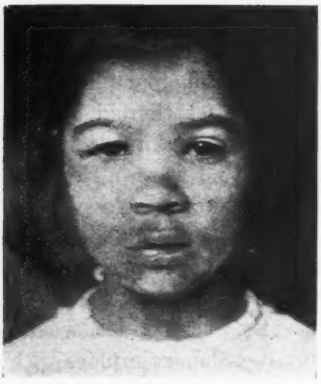

Fig. 80.—Case II. Before treatment, March, 1921. Note stupid appearance, saddle-nose, thick, protruding lips, straight, coarse hair.

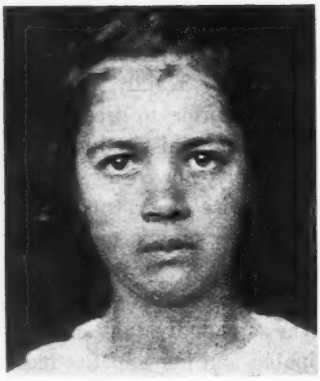

Fig. 81.—Case II. Six months after beginning treatment with thyroid extract. Extraordinary change in features and expression. Note especially luxuriant, glossy, curly hair.

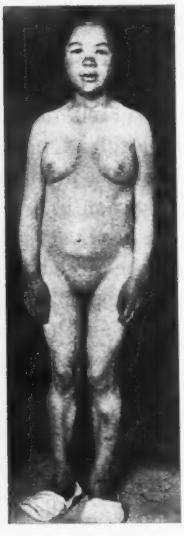

Fig. 82.—Case II. Appearance before treatment, March, 1921.

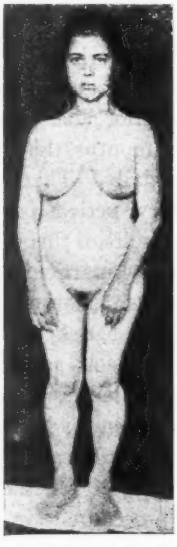

Fig. 83.—Case II. One and one-half years later.

instance, still others apparently not influenced very much. The outcome would seem to depend, as Gordon states, on the amount of thyroid deficiency, the time of the onset of the treatment, the age of the patient, and the regularity with which the treatment is carried out, together with the length of time under treatment, the secret of success, therefore, being early diagnosis with early and long-continued treatment. Mental defects seem most stubborn in the face of therapy. Some patients always remain a few years behind others of their age, some make no progress whatever, while others develop to a certain mental age and then remain stationary.

It is hoped that the above 2 cases will encourage physicians to search for such patients in their communities, and it seems reasonable that the brilliant improvement as demonstrated by the accompanying photographs will make those who read this article constantly on the alert for instances of adult and childhood myxedema.

Organotherapy and pluriglandular treatment is the latest therapeutic orgy of our profession. Much of it is innocent and well-meaning, but it is misguided and lacking in sound foundation. Some of it is downright commercial, vicious, and disgraceful. There remain some carefully controlled attempts with certain products that may develop into valuable procedures when sufficient evidence has been painstakingly collected. However, thyroid and thyroxin therapy is conspicuously successful and based on sound scientific methods, and finds its most brilliant application in the two conditions described above, namely, adult and childhood myxedema.

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DIET IN CERTAIN INTESTINAL CONDITIONS

MANY times we find ourselves looking far ahead, endeavoring to catch the first glimpse of some possibly unusual condition, when, if we lower our eyes to the foreground, we find some extremely common conditions easily overlooked because of their commonness and yet none the less discomforting to the patient.

It is for this reason I am inviting your attention to the present case, one of the most common found in the clinic.

Mrs. B. is thirty-five years of age; her complaint is of constipation and headaches existing many years.

The *family history* was negative save for the fact that her mother had chronic headaches.

As a child she had measles and scarlet fever.

She had one attack of influenza in 1919 and was in bed eight days.

The menstrual history was quite normal. She has given birth to 2 children, full term; no other pregnancies.

The appetite is good, sleep good; she does not arise at night. The weight is increasing. Bowels always constipated. Uses tea and coffee in moderation. No drugs, alcohol, or tobacco.

Present Illness.—As far back as she can remember she has always taken cathartics, usually two to three times a week. Cathartic after cathartic has worn out its usefulness until the list has been exhausted. Occasionally she has gone to a physician requesting a new physic, and a prescription has answered for a time, only later to be discarded with the others. The constipation seems to be increasing, and the headaches, frontal and vertical, come more frequently. These headaches are of

the migraine type, start in the morning and increase in severity until night, when pain is localized behind the right eye. Nausea and vomiting are at times present. The headache passes away with a night's sleep, but during the succeeding twenty-four hours the patient feels weak. A brisk purge is usually taken the day of the headache, and the passing of the pain in twenty-four hours is usually attributed to this medicine. What is called constipation is a lack of a movement without the aid of medicine. Two or three days may pass and then some cathartic is taken. Occasionally a hard, dry movement is had, and this is interpreted as meaning more physic is necessary. No more than two days are allowed to pass without something being taken, and lately it has been the rule to use a medicine every other day.

There is no abdominal or back pain; no tarry stools, no evidence of pus, but at times mucus is present.

On physical examination we see a very well-nourished woman, looking the age stated. The skin and appendages are of normal appearance, sclera clear; eye reflexes normal; nose clear; teeth well cared for, tonsils small, but pharynx appears rather congested and moist. Thyroid not enlarged. Lungs clear; heart of normal size—sounds clear, rhythm regular—rate 80; blood-pressure 130/85. The abdomen is rounded, skin shows slight dermatographia; liver and spleen not enlarged. The large bowel can be felt, especially the cecum, which is large and soft, and the descending colon, which gives the impression of a small firm cord. There is no particular tenderness. The pelvis is normal. The deep reflexes are present and equal.

Specific gravity of the urine is 1018; faintest possible trace of albumin, no sugar, indican slightly in excess, no casts, and an occasional leukocyte.

A gastric analysis revealed a normal acid curve rising to an apex in an hour and a quarter, then steadily declining.

x-Ray screen of digestive tract shows a rather low stomach lying in the left quadrant with the pylorus on a line with the iliac crests, movable, peristalsis normal, and duodenal cap large and smooth. In six hours there is no gastric residue,

the head of the meal is in the terminal ileum. In nine hours the cecum is filled and movable. In twenty-four hours most of the barium is in the cecum and ascending colon, with small masses in transverse descending colon and rectum. An enema passes readily to cecum. Haustra seen throughout, but in transverse colon and especially in the descending colon appear very narrow.

The stool is well digested; it shows no fermentation and microscopically appears Gram negative with some Gram-positive rods.

The examination reveals a rather healthy woman with very little sign of disease, but showing the following minor points: a mildly inflamed pharynx, a palpable colon, a slight dermatographia, indican in the urine, a spastic colon, and a putrefactive type of stool.

And now regarding her diagnosis: As to headaches in general, the cause is legion. To go into a discussion of causes would occupy too long a period. Suffice it to say the most likely cause is an intoxication.

I wish to speak more in detail on the constipation. It is very necessary to get each individual's detailed story of his constipation in view of the fact that everyone has a different idea of what constitutes constipation. If our knowledge of the physiology of the digestive tract were as universal as our knowledge of the necessity of eating, and it should be, the discussion of constipation would become a lost art. Some consider constipation as a failure of a movement daily, some call a hard movement constipation, while others use the same term if the movement is not of a definite volume and consistency. Consequently, it is readily seen we must take each case and consider it by itself. One must not only know the immediate effect of catharsis, but the subsequent effect. A brisk purge removes a large volume from the bowel. This volume is necessary to maintain the normal peristaltic action. After the sudden removal of this volume it may take from two to three days to return to what the musculature and reflex action demands. In the meantime there is no movement and another purge is

taken before a normal condition is reached. Thus is kept indefinitely a vicious circle.

These people frequently show a descending colon of small caliber with some haustra present, and are labeled spastic constipation, and treated as such. The assumption is that the spastic condition of the large bowel comes from overstimulation of the vegetative nervous system, and I feel that this stimulation is caused most frequently by some protein intoxication. The toxin can come from local infections in mouth, throat, nose, lungs, appendix, gall-bladder, or putrefactive bacterial products resulting from the action of the bacteria on food in the intestinal tract.

From the laboratory we have learned that certain bacteria break up complex protein into amino-acids, such as histidin, which are in themselves toxic to the body. Normally these bacterial products are taken up by the liver, changed into harmless etherial sulphates, and excreted by the kidneys in a form recognized as indican. Escaping through the liver into the general circulation, these by-products will irritate the vegetative nervous system and cause other unpleasant symptoms, as mental irritability, headaches, etc.

And now with regard to the presence of indican in the urine: Its presence means intestinal putrefaction, bacterial in origin. Large amounts probably can be interpreted as meaning the liver is able to destroy about all the harmful elements. With the presence of smaller amounts of indican some putrefactive products may be escaping into the body. The absence of indican would mean one of two things, either no intestinal putrefaction, or that the liver by failing to detoxicate the product allows the toxin to escape into the general circulation.

The putrefactive organisms enter the intestinal tract in numerous ways. The food of the child may be contaminated by a parent harboring these bacteria. A nasopharyngeal infection may supply the organisms that subsist on the protein of the food.

To summarize the findings in our patient, we may connect facts as follows: She is suffering from periodic headaches which

seem to have a toxic origin. From the presence of dermatographia, spastic colon, indicanuria, and a putrefactive stool we feel the origin may be in the intestinal tract. This may come from her chronic pharynx or may date back to childhood as suggested by headaches in her mother. The constipation in itself is probably habit, increased by the religious use of cathartics, as shown by the *x*-ray examination. And this brings us to treatment. We seek a cure by removing the cause. Our attention is directed to removing a troublesome strain of bacteria from the intestinal tract. Can this be accomplished by purging? No. It has been shown by Whipple[1] and others that cathartics and irrigations do not remove the flora. These particular bacteria live solely on protein and particularly on meat products. Putrefactive bacteria are not usually found in the intestines of infants. Here we have a definitely acidophilic type. When this type changes the infant becomes ill and is toxic. In 1919 Torrey[2] showed by feeding experiments on dogs that he could change the type of intestinal flora by change in diet. On a starch-sugar diet the putrefactive bacteria disappeared. This was definitely assured by the presence of lactose. Four days were sufficient to make the change. From the foregoing we have evolved a diet to bring the desired effect. No meat or meat products are allowed for four days. We exclude fish, shellfish, chicken, soups, and gravies from meat stock. A minimum of protein is allowed for the daily body needs, about 40 gm., taken as white of egg (cooked) or cheese. Fats, green vegetables, fruits, and an abundance of starch from all sources are allowed. In addition, at least 1 tablespoonful of lactose (milk-sugar) is taken with each meal, used as cane-sugar, and used with cane-sugar according to the patient's taste.

On the completion of these four days, three days of meat diet follows. No milk-sugar is taken and starches are materially reduced, green vegetables, fats, and fruits remain unchanged. This alternation of diet is continued for weeks. On the meat-free days the stools become more bulky and light in color. Stained smears show a definite change in the bacterial picture. On the meat days the stool is darker and more firm.

The alternation is for two purposes, first, to cause a growth of intestinal bacteria, facultative to either protein or carbohydrates, which are quite harmless, and second, the patient does not feel he is being deprived of foods normally enjoyed. As you will see by the printed list, a copy of which is given the patient, this diet comprises the foods usually found on the table each day.

ALTERNATING DIET

First Four Days. Diet (1)

DO NOT EAT: Meat, which includes all flesh in any form, as beef, chicken, fish oysters, ham, bacon, or any soup or gravy made from meat stock.

EAT:
Starchy foods—Bread, potatoes, rice, macaroni, sago, crackers, cornstarch, pastry, mush, cereals, milk, ice-cream, sugar.
Fats—Butter, cream, lard.
Green Vegetables of all varieties.
Proteins—Eggs, 3-4 daily, (cooked), cheese (3-4 cubic inches).
Fruit—as desired.
Important: Take at least one tablespoonful of sugar of milk with each meal, using it as you would cane sugar.

Three Days (Following above four days) Diet (2).

EAT:
All kinds of meat, in any form, at least twice a day.
Only one piece of bread with each meal.
Only one small potato, once a day.
Only one tablespoonful of rice or macaroni at meal when no potato is eaten.
Eat green vegetables without flour sauces.
Desserts of fruit and gelatin, but no pastry.
Eat very little sugar.
Use no milk sugar.
Milk taken in small quantities only, if at all.

On completion of Diet (2) return to Diet (1) etc.

NOTE: It is best to eat three or four times a day. Tea and coffee used according to one's habit.

By this diet we establish a harmless intestinal flora, but that by itself will not change the constipation habit. As has been said many times, in probably 99 per cent. of the cases the apparent inactivity of the bowels is not due to anything pathologic in the digestive tract. The trouble lies in wrong ideas most people entertain regarding the physiology and func-

tion of the digestive organs. To attain success it is very necessary to convince the patient we have full knowledge of the condition of his particular digestive system. This is accomplished by the varied examinations at our command, as mentioned above. We are thus in a position to assure him that no actual disease of the intestines exist, and I feel this is most important. It is then very necessary to teach the patient the true facts regarding the bowel function, and finally convince him of the value and necessity of habit, which should follow breakfast each morning, and the harmful effect of cathartics which truly defeat the very purpose for which they were taken.

Our patient had been placed on this diet a few weeks ago and definitely instructed regarding the proper bowel habit. She has taken no cathartics or enema, and after the second day she has rarely passed a day without a movement. She has had but one headache, and that one was less severe than usual and passed just as quickly as when she has taken a purge. A specimen of urine showed no indican. She will continue this diet a few weeks, and then be instructed to eat what she wishes for two weeks, and follow the diet again two weeks. This is simply to insure no return of the putrefactive bacteria.

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A CLINICAL COMPARISON OF APLASTIC ANEMIA, IDIOPATHIC PURPURA HÆMORRHAGICA, AND ALEUKEMIC LEUKEMIA BASED ON STUDIES OF THE BONE-MARROW

IT might seem at first thought that the conditions mentioned in the title are well enough defined as clinical entities, so that confusion should be avoided. As a matter of fact, there are cases encountered from time to time that do not conform strictly to type and where it is difficult to make a diagnosis without knowledge of the disease changes taking place in the marrow.

Let us consider first aplastic anemia. The disease has a symptomatology dependent upon an aplasia of the bone-marrow. If we can find an etiologic factor we say that we are dealing with an aplastic anemia secondary to the causative agent. If no etiology can be found we term it idiopathic aplastic anemia, a disease condition first described by Ehrlich. This latter condition is more common in young adults, runs a downward and rapidly fatal course of three to six weeks' duration, rarely as long as six months. It is characterized by a profound anemia of the non-regeneratory type and symptomatic purpura hæmorrhagica.

In secondary or symptomatic aplastic anemia we recognize certain causative agents, as, for example, benzol-poisoning or bacterial toxins. Both types, however, have the same kind of a blood-picture, namely, an anemia due to failure of the marrow to produce new cells and to a rapid using up of those

already present in the blood-stream. Roentgen rays and radium possess a destructive action on the hematopoietis tissues which terminates in an aplastic marrow if the individual is subjected to these agents over a long period of time. At times the so-called acute hemolytic anemias may show the terminal picture of marrow aplasia. These anemias may be caused by hemolytic poisons, as acetanilid, pyrodin, trinitrotoluol, and other coal-tar derivatives. Streptococcic septicemia may produce an acute hemolytic anemia which rapidly exhausts and depresses marrow function, finally giving rise to an aplastic blood-picture. Rarely pernicious anemia may as a terminal event show extensive marrow aplasia. There is also a group of anemias termed "myelophthisic," which depend on invasion of the marrow by tumor-cells or the abnormal cells of leukemia. Medullary metastasis of a primary carcinoma of the prostate or breast or a hypernephroma may crowd out the normal marrow elements to such an extent that a secondary aplastic anemia results, with diminution of the platelets, and purpura hæmorrhagica. The same mechanical crowding out of marrow elements may take place in the leukemias, and if one happens to be dealing with the aleukemic or leukopenic phase of the disease the picture is confusing, as the dominant symptoms are a marked diminution of the red cells, white cells, and platelets with purpura hæmorrhagica and hemorrhages; in other words, the picture of an aplastic anemia. Hence we see that all of these different clinical entities through their degenerative effects of the bone-marrow may at some phase of their development present a distinct similarity to idiopathic aplastic anemia, and they may be confused with it unless the etiology is carefully searched for and uncovered. True aplastic anemia, however, as stated at the beginning, is a disease of young adult life, progressing rapidly and terminating in a few weeks or months. The cause is not known, in contradistinction to secondary aplastic anemia. The clinical manifestations are marked anemia and secondary purpura. Stomatitis and a febrile reaction commonly occur. The spleen is not enlarged and generalized glandular enlargement is not a feature. The blood-picture

shows little or no evidence of regeneration of the formed elements, nor is there evidence of blood destruction as gaged by the excretion of urobilin. The anemia is marked, the red cells may reach as low as 500,000, with an accompanying leukopenia consisting of an absolute diminution of the polynuclear elements and a high relative lymphocytosis, at times reaching over 90 per cent. The platelets are markedly diminished. Ordinary blood-smears show the red cells little changed from normal size and shape. Reticulated red cells, polychromatophilia, and nucleated red cells are rare or absent entirely. The color-index averages less than 1. At autopsy the marrow is fatty in the long bones and hypoplastic or aplastic in the flat bones.

Let us next turn to purpura hæmorrhagica, a condition which should always suggest the possibility of an underlying primary disease. As a secondary manifestation it is common in a variety of diseases, as smallpox, scarlet fever, acute infections, as streptococcus and staphylococcus, blood-stream infections, meningococcic septicemia, tuberculosis, nephritis, cirrhosis of the liver, the leukemias, and aplastic anemia groups. The idiopathetic type of purpura hæmorrhagica is common in young adults. The condition, as defined by Minot, is characterized by hemorrhages from the mucous membranes, petechiæ or ecchymoses of the skin, a prolonged bleeding time, a non-retractile blood-clot, and a markedly reduced platelet count. This reduction in blood-platelets was first noted by Denys in 1887, and it is a striking and constant feature, accounting for the clinical manifestations of hemorrhages from the mucous membranes and into the skin. The anemia which follows the onset of the disease is, for the most part, a posthemorrhagic anemia of the secondary type. However great the loss of blood, due to repeated large and small hemorrhages, there is an attempt on the part of the marrow at regeneration, as evidenced by moderate polynuclear leukocytosis, both relative and absolute, occasional normoblasts, and the presence of reticulated red cells. This compensatory effort on the part of the marrow varies according to the degree of primary (toxic) and secondary (hemorrhagic) insult to which it is subjected. The blood-

picture therefore varies within certain limits, and we may get a group of atypical or intermediate cases approaching aplastic anemia in type.

At autopsy the long bone-marrow is reddish in typical cases due to increased effort thrown upon the erythropoietic tissue to compensate for the blood loss. Such marrow is cellular, both the red and white cell elements being increased with a decrease of the normal fatty tissue. A few cases studied show the progenitors of the blood-platelets, the megacaryocytes of normal appearance, with no diminution of their relative numbers. It is not known whether the platelets are destroyed in the circulation, as can be experimentally produced in rabbits by injection of antiplatelet serum, or whether a specific toxin acts selectively upon the giant-cells, decreasing their numbers or destroying their physiologic function of budding off new platelets. There have been cases described that suggest the presence of a toxin with a selective action primarily on the platelets, and later on the red and white cell elements, resulting in a partial or total aplasia of the marrow and producing a terminal aplastic anemia.

Now let us turn to the last member of this group of clinically related diseases, namely, acute lymphatic aleukemia. Giving, as it does, a picture of anemia, purpura hæmorrhagica, fever, and stomatitis, might lead one to suspect either aplastic anemia or idiopathic purpura hæmorrhagica. However, the presence of an enlarged spleen and generalized glandular enlargement in lymphatic leukemia serves as a help in differentiation. There are cases, however, where the lymph-gland hyperplasia is localized and therefore not likely to attract attention. The blood-picture in leukopenic leukemia may be similar to that of aplastic anemia in that there is marked reduction in the red cells, a leukopenia, and a diminution of platelets. These blood findings are dependent on the crowding out of the red cell elements and giant-cells by the lymphoid cells. The islands of tissue that remain in the marrow show hyperplasia due to a compensatory effort at regeneration as shown by the presence of nucleated red cells in the peripheral blood. Just why it is

that a bone-marrow densely infiltrated with lymphoid cells does not send out greater numbers of such cells into the peripheral blood-stream is not known. It would seem as if the mechanism that delivers cells into the blood-stream is either inhibited or paralyzed in these cases.

In a superficial manner, then, we have compared three diseases of the blood-forming organs that have much in common as regards symptoms, but are based upon different pathology in the bone-marrow. As we have seen in true aplastic anemia, the marrow of the long bones is fatty throughout and devoid of the small islands of hematopoietic tissue normally seen scattered through the fatty meshwork. The marrow of the long bones in idiopathic purpura hæmorrhagica is more cellular and may be even slightly reddish, depending on the hyperplasia present. The hyperplasia, in turn, depends on the effort put forth by the marrow to make up for blood loss by the hemorrhages which play such a prominent part in this disease. Lymphatic leukemia of the aleukemic type, while showing relatively few lymphoid cells in the peripheral blood, shows in the marrow marked hyperplasia of these elements. A smear from such a marrow is solidly packed with these large non-granular lymphoid cells. The red cell tissue shows varying degrees of hyperplasia depending on the amount of encroachment and crowding out by the leukemic cells, as they infiltrate the marrow cavity.

These differences in the cellular content of the marrow may offer another clinical means in the diagnosis of each of the above diseases if they hold true to type. Variations in type, however, as previously mentioned, are common in plastic anemia and idiopathic purpura hæmorrhagica. We are interested in the possibility of using the bone-marrow as a help in clinical differentiation because of our attempts at intra-vitam bone-marrow study. Following Ghedini's work on bone-marrow puncture we have used this method to study the marrow of the tibia in about 30 cases of various diseases. Our work is now at press and will appear in the October number of the Archives of Internal Medicine.

In 2 of the 3 cases which we are reporting here we used bone-

marrow puncture, as we felt that such a procedure might give us more valuable diagnostic and prognostic information.

Case I.—Patient a child, male, aged four years.

Family history negative.

Past history.—Nothing significant except influenza in 1919.

Complaints.—Bleeding from nose. Pallor and weakness.

Present Illness.—One month before admission to hospital the symptoms of present trouble began with a mild febrile attack. Two weeks later another abnormal rise of temperature occurred and the child became progressively pale and anemic in appearance. Three days before admission a large nasal hemorrhage occurred which was arrested with difficulty.

Physical Examination.—Child well developed and nourished. Color of skin and mucous membranes pale.

Eyes: Pupils equal, react to l and d.

Ears: Negative.

Nose: Bloody crusts about the nares.

Mouth: Lips swollen. Ecchymotic areas in mucosa of mouth and about gums.

Glandular system: The cervical lymph-nodes are moderately enlarged in both anterior and posterior triangles.

Heart: Negative except for systolic murmur heard at base.

Chest: Lungs showed a few râles at the bases of both posteriorly.

Abdomen: Rounded, symmetric. No tenderness. No dulness in flanks. Liver not palpable. Spleen enlarged about 2 fingerbreadths below costal margin. No ecchymosis noted in skin.

Blood-count: Hemoglobin, 32 per cent.; red cells, 1,790,000; white cells, 850.

Differential: Polymorphonuclears, 1 per cent.; large mononuclears, 2 per cent.; lymphocytes, 97 per cent.

The red cells show anisocytosis, poikilocytosis, achromia, microcytes. No nucleated red cells, platelets markedly reduced.

The admission temperature was 40° C., remained elevated for five days, and dropped by lysis.

Marrow puncture: On the third day after admission tibia was punctured. Marrow was fatty. No myeloid cells were seen in any of the smears. A few lymphocytes were present, no nucleated red cells. Cultures from the aspirated marrow remained sterile after seventy-two hours.

Transfusion: Citrated blood was given on the third day after admission.

Blood-count (seven weeks after admission): Hemoglobin, 62 per cent.; red cells, 3,790,000; white cells, 11,500.

Differential: Polymorphonuclears, 60 per cent.; lymphocytes, 29 per cent.; large mononuclears and transitionals, 6 per cent.; myelocytes, 5 per cent.

Macrocytes and microcytes were present with moderate poikilocytosis. Reticulated red cells, 3 per cent.

Shortly after this blood-count child returned home, relapsed, and in spite of transfusion died of a progressive anemia with purpura. No autopsy was performed.

In our consideration of this case the clinical picture is atypical of acute aplastic anemia. The onset with fever, followed by an intense anemia, suggests infection profoundly injuring the bone-marrow. We attempted to rule out bacterial localization in the long bone-marrow by cultural methods, which proved sterile. The variation in size and shape of the red cells with a predominant microcytosis suggests the smear picture of a secondary anemia for which no etiology is forthcoming. (The nasal hemorrhage was not of sufficient extent to be classed as the cause.) The marked anemia, leukopenia with relatively high lymphocytosis, and diminution in platelets lend weight in favor of aplastic anemia, but the typical remission after transfusion with such a marked change in the blood-count and evidence of both white and red celled regeneration is foreign to the picture of aplastic anemia. The marrow studied conformed to the aplasia of this disease. It was so definitely aplastic for a child's marrow of four that we felt the prognosis decidedly grave. We have no way of reaching the normal red marrow of the flat bones during life. In this case as in others we must assume its character by analogy with the condition found in

the long marrow. From our marrow studies we ruled out leukopenic lymphatic leukemia; we made a tentative diagnosis of acute aplastic anemia and were much surprised at the child's remission; the subsequent relapse and rapid downward progression suggest marrow aplasia as the patient's termination.

Case II.—Patient C. H., aged twenty-four. Iron worker, No. 37,254, April 3, 1922.

Complaint: Bleeding from bowels and gums.

Family history negative for hemophilia.

Past History.—Born in Carlsbad, N. M., 0–5; Arizona, 5–15; Mexico, 15–17. In navy, 17–21, traveling to Hawaii, Alaska, Cuba, Philippine Islands; 21–24, various parts of U. S. mostly Pacific Coast.

Occupation: Iron worker, structural riveting, etc., on large buildings; worked on copper smelter in replacing iron structure which was eroded by H_2SO_4 fumes. These fumes were so concentrated that patient had to have a new set of work clothes every night. He was exposed to these fumes for about three months. Since this work, which he states was the beginning of present illness, he has been working in mountains, lumbering camps, etc.

Married four years, wife alive and well; 1 child alive and well aged eighteen months; no miscarriages.

Diseases: Chicken-pox, measles, mumps (no orchitis), whooping-cough, pneumonia; typhoid fever when sixteen, in bed three weeks; no malaria. Venereal: Question of neisserian infection six years ago.

Present Illness.—Eighteen months ago, about November, 1920, just after three months' work on structural steel at an Arizona copper smelter, as stated under past illnesses, patient noted small quantity of blood and mucus in stools—about seven to eight movements per day, lasting for one week; no gastric pain, nausea, or vomiting; no symptoms except frequent stools. He was in good health from this first attack of diarrhea up to second, which was about January 1, 1922—frequent stools with mucus and blood again persisting up to present,

with an occasional tarry stool. During the past month (March) patient has been bleeding from gums in gradually increasing amounts. He has during this time become weak, dizzy, and dyspneic. Hemoglobin has ranged between 47 and 60 during past month; 20 pounds loss of weight in past three months.

Physical Examination.—Skin pale, scattered, small hemorrhagic pin-point spots.

Eyes: Conjunctiva show small pin-point hemorrhages.

Ophthalmoscopic: *Right:* Nerve head normal color, no hemorrhages. Some pulsation of arteries, which seem enlarged. *Left:* Edge of disk slightly blurred. Vessels smaller than on right.

Mouth: Two teeth missing; no caries; signs of bleeding at gum margin; tonsils negative.

Glands: Small shotty glands in left submaxillary triangles; few shotty glands palpable beneath anterior border of right trapezius; few in both inguinal regions and in left epitrochlear.

Lungs negative.

Heart: Size normal, cardiopathic angle normal. P. M. I. fifth interspace 1 cm. inside nipple line. Sounds: Systolic murmur which accompanies but does not obscure the first sound. Second sound clear. A_2 is greater than P_2. Murmur transmitted toward axilla and to great vessels of neck. Blood-pressure: Systolic 110, diastolic 75. Pulsation of peripheral vessels marked.

Abdomen: Spleen and liver not palpable. Marked tenderness on deep palpation about 1 cm. below umbilicus in midline.

Reflexes: Negative.

Wassermann in serum (April 4, 1922): Negative.

Blood-count: Red blood-cells, 1,528,000; white blood-cells, 4400; hemoglobin, 57 per cent.; color-index, 1.9.

Differential: Polymorphonuclears, 65 per cent.; small mononuclears, 19 per cent.; large mononuclears, 4 per cent.; transitionals, 11 per cent.; eosiniphils, 1 per cent.; basophils, 0 per cent.

Red cells show variation in size, no nucleated reds. We have no record of reticulated cell or platelet count.

Stool examination: Flecks of bright blood, mucous shreds, active Amœba dysenteriæ found; no cysts. Dr. M. C. Cheney.

Urine examination negative.

Gastric analysis showed free and total HCl slightly diminished; many red blood-cells in sediment of gastric contents.

Proctoscopic examination showed in lower 6 inches of rectum three raised bleeding ulcers reddened about periphery about 1 cm. in diameter.

Blood-culture negative.

Stool-culture: Proteolytic flora, negative for bacteria of typhoid dysentery group.

April 10th: Bleeding time, four minutes, thirty seconds, (Duke). Coagulation time, nine minutes, thirty seconds (Lee and White).

Fragility: Hemolysis began, 0.40; complete, 0.35.

Record of blood-count:

April.	Red blood-count.	Hemoglobin.
4th	1,528,000	37
10th	1,248,000	38
13th	1,310,000	35
15th	1,420,000	38
17th	1,920,000	45 transfusion 400 c.c.
21st	1,760,000	37
25th	2,520,000	35 transfusion 400 c.c.
27th	2,360,000	45

Note: There was a febrile reaction reaching as high as 38° C. during first four or five days following admission. Afterward there were several slight rises to 37.4° or 37.6° C.

This patient asked to go home for a short visit, to return in two or three weeks for readmission. He became rapidly worse, dyspnea and weakness being marked features, and in about three weeks he died. No autopsy was held. While he was in the hospital a marrow puncture was performed. The marrow from the tibia was fatty and devoid of cells. (See Fig. 84.)

This case does not conform in all respects to a typical case of aplastic anemia, but inasmuch as no etiology could be found and the marrow obtained by puncture was aplastic, or not responding to the stimulus that such a marked anemia would

naturally call forth, we felt that it undoubtedly belonged in the aplastic group of anemias. His marrow had slight powers of regeneration, as noted by the increase of red cells and hemoglobin, but the trend was progressively downward, with no definite remission. The etiologic bearing on the amebiasis, with ulcerations of the colon and loss of blood from this cause,

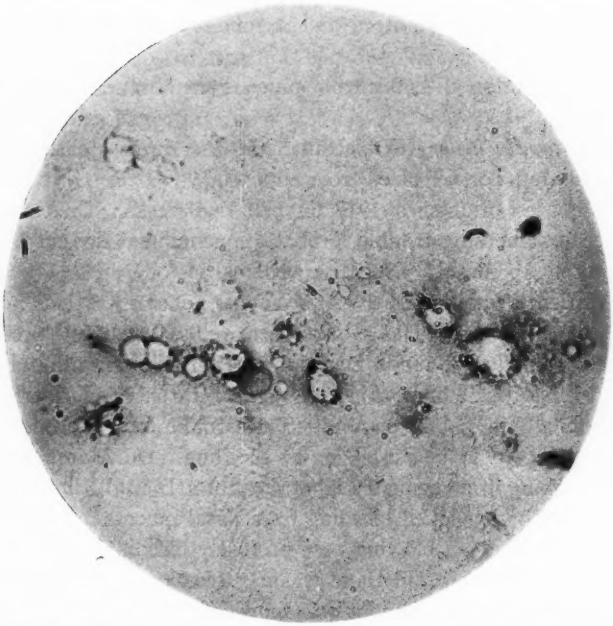

Fig. 84.—Case II. Aplastic anemia. Fatty marrow from tibia. Shadows of cells present are due to red blood-cells, result of trauma. Considering degree of anemia present, this marrow is non-regeneratory.

was carefully weighed and discussed, but as the anemia did not improve after the amebæ were apparently removed and bleeding from the ulcerations checked, we concluded that this infection was incidental. The question of the part played by inhalation of sulphuric acid fumes was investigated. We wrote to the physician in charge of the copper smelter where the patient had been exposed to these fumes. He stated that during

his connection with the smelter over a period of several years he had never come in contact with cases of marked anemia among smelter employees. Our prognosis from a study of the marrow of the tibia, showing no cellular response to the marked anemia present, was that improvement could scarcely be looked for.

Case III.—B. F., aged twenty-one. Admitted March 7, 1922.

Complaints: Bleeding from mucous membrane of nose and mouth.

No *family history* of bleeding. Mother bruises easily from trauma, but doesn't bleed from cuts.

Diseases: Influenza 1918, in bed two weeks. On October 7th had some lung trouble, probably pneumonia; doesn't know definitely about this. Negative venereal history.

Patient's habits negative. Accidents none; operations none.

Present Illness.—Has always been well. Just before present illness gained 10 pounds in weight. Past five years has been troubled with itching skin; at night scratched considerably; occasionally an abrasion and crusts would form at once, so that there would be no oozing or bleeding. On March 1st he was working in a chemistry laboratory at a Dental School when he suddenly developed bleeding from nasal mucosa. The blood would clot, but on blowing nose profusely bleeding would start. From March 1st to 3d there was a succession of bleeding and clotting; each time the clot was longer in forming. On March 1st during night he scratched his right shoulder. When he awakened in morning there was a small reddish area bleeding, and the sheet on which he was sleeping was heavily blood-stained. Several of the reddish spots formed over back of clot and right shoulder continued to bleed during day of March 2d. He also noted small reddish areas appearing in the mucous membranes of the mouth and lips, and several of these have become bleeding points, also some on tongue. Also bleeding points have appeared in skin over body where he has scratched himself. On March 1st he was wrestling with fellow student and right wrist struck

window sill. The wrist turned "black and blue," although the blow was very slight. No previous history of ecchymosis due to injury. No history of gastro-intestinal symptoms, of joint disturbances, hematuria, etc. No previous skin trouble except as mentioned.

Physical examination was essentially negative.

Examination of nose and throat on entry showed profuse oozing from mucous membranes of left nostril, with some clotted blood. Right nostril was not bleeding, but showed areas encrusted over, also evidence of the cautery having been applied to the mucous membranes of this nostril. On lower lip are six or eight hemorrhagic blebs in size from 0.3 to 0.5 cm. in diameter raised from surface about 4 mm. some dry and dark, others brighter red and oozing blood. These areas are seen to be due to subcutaneous and submucous bleeding. On dorsum of tongue is a bleeding-point. In mouth are twenty-five to thirty small bleeding spots. In skin of body are many small discrete reddish spots which are small subcutaneous hemorrhages. In some areas they are larger and diffuse. Thrombplastin and 1 : 1000 adrenalin applied locally, also nares plugged; 15 c.c. whole blood given from brother. Site of injection (one needle puncture) bled from eight to ten minutes.

March 8, 1922: Patient grouped for transfusion belongs to Group II.

Blood-count: Hemoglobin, 65 per cent.; white blood-cells, 6300; red blood-cells, 3,740,000.

Differential: Polymorphonuclears, 82 per cent.; small lymphocytes, 14 per cent.; large lymphocytes, 4 per cent.

There is considerable pallor of red blood-cells, slight difference in size, no difference in shape; practically no platelets seen. Patient transfused, citrated method, 425 c.c. of blood.

March 9, 1922: Purpuric areas clearing on back and shoulders, also on tongue. No new spots seen. He seems improved today.

March 10, 1922: Bleeding from nose. Ecchymotic areas in mucosa of pharynx; lips edematous. No evidence of bleeding from gastro-intestinal tract. Transfusion, 415 c.c. whole blood, by Luer method. This method arrested bleeding.

Urine: Slightest possible trace of albumin; no sugar; 4 to 5 white blood-cells to high dry field. No red blood-cells.

Bleeding time sixty minutes.

Coagulation time, 11 mm. tube, not paraffined. Completely inverted in ten minutes.

March 11, 1922: Complains of headache, weakness, and sense of dulness and deafness, especially left ear.

Bleeding from right nostril today. Rectal temperature, 39.2° C.

Blood-count: Hemoglobin, 30 per cent. (Sahli); 40 per cent. (Tallquist); red blood-cells, 2,552,000; white blood-cells, 1600. No signs of regeneration. Platelet count, 18,000 (Wright and Kinnicutt).

Fragility of corpuscles: Began, 50; complete, 40.

March 12, 1922: No bleeding from nostrils; is swallowing some blood. New hemorrhagic bleb on lower lip and bleb on roof of mouth; also bleb about 0.5 x 1 c.c. on left margin of tongue; some oozing from these blebs.

Physical examination practically negative except for loud blowing systolic murmur all over precordia, best in mitral and pulmonic areas; not transmitted to axilla. Positive Oppenheim on left; Babinski positive on right. Transfusion, 550 c.c. citrated blood.

March 14, 1922: Oozing from both nostrils. Temp. 40° C. Very weak. Transfusion, 475 c.c. citrated blood.

March 15, 1922: Deafness both ears. Edema of extremities. Temperature 40° C. No new purpuric spots.

March 16, 1922: Direct transfusion, 600 to 900 c.c. blood. Rectal temperature 41.3° C. Tongue edematous.

March 17, 1922: Very weak. Rectal temperature 41.4° C. Pulse, 140. Vomiting. Generalized edema.

March 18, 1922: Died.

Postmortem Examination.—Autopsy diagnosis: Septicemia—Streptococcus hemolyticus. Areas of hemorrhage lower lobes both lungs. Petechial hemorrhages epicardium, renal pelvis, and subserosa of stomach. Hemorrhage from nose and ulcer

nasal mucosa on right. Slight cardiac hypertrophy and dilatation. Slight chronic interstitial nephritis.

This case represents a fairly typical case of idiopathic purpura hæmorrhagica. If we assume that the Streptococcus hemolyticus was present during life and was not a terminal infection (blood-cultures during the course of the illness were negative)

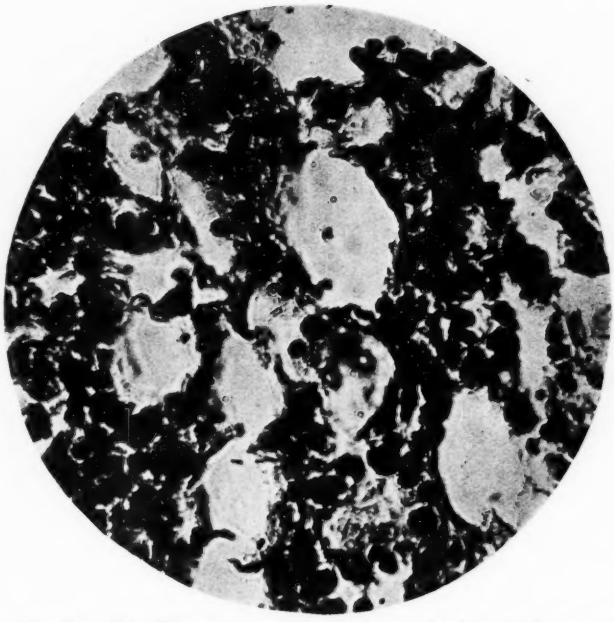

Fig. 85.—Case III. Rib marrow. Purpura hæmorrhagica. This marrow is cellular and does not suggest an aplastic marrow.

we would have to place the purpura hæmorrhagica secondary to streptococcus septicemia and the case would correspond very closely to one reported by Cabot in Case Records of the Massachusetts General Hospital, November 1, 1921. However, we have no right to assume that such an infection was present, as blood-cultures were negative. The bone-marrow here was not aplastic, as can be seen from Fig. 85 rib marrow

and Fig. 86 from the femur. The peripheral blood showed very little effort at regeneration, but the disease ran such a rapid course that it had very little opportunity to respond. Had the patient survived for a longer period it is possible that a considerable marrow aplasia would have resulted. The case represents an intermediate type, with very little marrow re-

Fig. 86.—Case III. Tibia marrow. Purpura hæmorrhagica. This marrow has a few cells. Not definitely fatty marrow. Compare with Fig. 84.

sponse, that approaches somewhat the aplastic anemia type. Many of the reported cases of the true idiopathic type are improved by transfusion and enjoy remissions in which they feel fairly well. Transfusions were of little avail here.

Our purpose in presenting the above cases was to call attention to certain variations from the type case that are bound to occur in the three groups of disease entities under consideration.

We make the statement that variations in type are bound to occur because the etiology of each of the types under discussion is unknown, and where such is the case classification must allow of considerable latitude. If we attempt to classify or diagnose these diseases according to symptomatology and clinical findings, confusion is likely to arise, especially between idiopathic

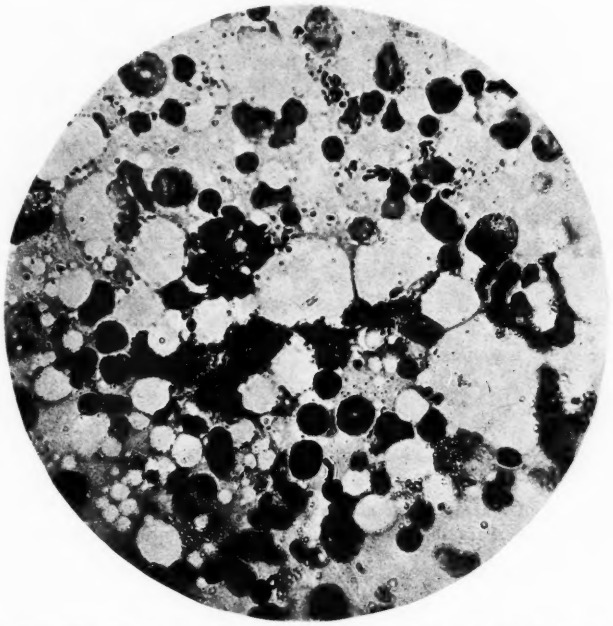

Fig. 87.—Marrow obtained by puncture from tibia, child aged two years. Hyperplasia in response to anemia.

purpura hæmorrhagica and aplastic anemia. The wise clinician reserves judgment and awaits the autopsy findings. If, however, marrow puncture will supply us with knowledge of the marrow pathology during life it will be a distinct aid in differentiation. We hesitated in the case of purpura hæmorrhagica above quoted to perform marrow puncture on account of the marked diminution of platelets and consequent hemorrhagic tendency.

We are indebted to Dr. Langley Porter for opportunity to study the marrow and report the findings of the first case

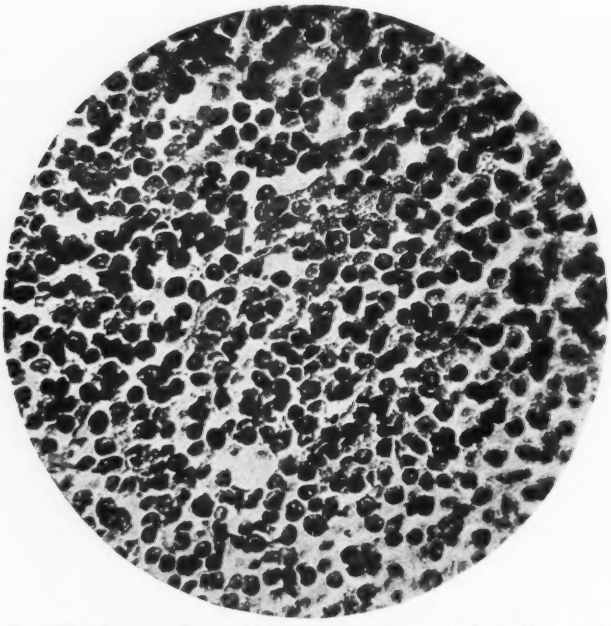

Fig. 88.—Marrow from child aged six. Lymphatic leukemia. Peripheral blood-smears showed non-leukemic picture until two weeks before death.

above mentioned. For permission to report the other 2 cases we are indebted to Dr. William J. Kerr, on whose service these patients were entered.

CLINIC OF DR. RICHARD W. HARVEY

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COMBINED SYSTEM DISEASE

SINCE Lichtenstern in 1884 pointed out the involvement of the spinal cord in cases of pernicious anemia clinicians have been interested in neuropathologic studies of numerous diseases in which combined sclerosis is a frequent finding. Such conditions as infectious diseases; poisons, such as lead, arsenic, alcohol, and ergot; leukemia and secondary anemias; pellagra, diabetes mellitus, senility, and others show neuropathologic changes similar to those of pernicious anemia. While the earlier studies limited the sclerosis to the cord, more recent findings relate to cerebral pathology, particularly in cases which occur with pernicious anemia. Furthermore, peripheral nerve changes have been described due to involvement not only of the ventral roots of the spinal nerves but also of the dorsal roots and ganglia.

Case I.—*Clinical Record.*—D. C., aged sixty; occupation, trapper and hunter. First admission to San Francisco Hospital April 25, 1919 to July 11, 1919. For about ten months the patient had complained of dyspnea, general weakness, paraesthesias of the extremities, and vomiting.

Examination showed pigmentation of the face, a lemon-colored tint of the skin, pyorrhea, and dental caries. A soft systolic murmur was heard over the heart. The liver was enlarged. The Wassermann examination of the blood-serum was negative. Blood-picture was that of pernicious anemia. Symptomatically the patient was improved at the time of his discharge. In October, 1919 the patient returned to the hospital showing the picture of the previous admission, but in a more striking degree. The heart rate had increased; the pigmenta-

tion of the skin deepened and the spasticity of the legs was more marked. Complete picture was that of a pernicious anemia: Hb., 40 per cent.; R. B. C., 1,420,000; marked anisocytosis and poikilocytosis; the lower extremities were extremely spastic and adductor spasm was present with advanced muscular atrophy. The patient died in June, 1920.

Anatomic Diagnosis.—Pernicious anemia; cardiac dilatation; chronic cystitis; slight chronic focal nephritis; moderate brain atrophy without arteriosclerosis; slight diffuse atrophy of the cord with degeneration in the posterior columns.

Neuropathologic Findings.—Subacute myelinic degeneration of the posterior and lateral columns and vacuolization of some ventral horn cells with eccentricity of nuclei and a slight perivascular softening in the cortical sections.

This case presents a clear picture of pernicious anemia with neurologic symptoms. Neuropathologic studies show cerebral, cord, and peripheral lesions. Etiologically it is to be assumed that some toxic substance reaches the central nervous system through the blood-vessels because it is about these that the primary degenerative foci are found; and following this primary destruction there is a secondary degeneration of the nerve tracts. The nature of the toxic substances is unknown, but in this case a focus of infection existed in the mouth cavity which may have been the source of the toxins.

Case II.—*Clinical Record.*—A. E. K., married woman, aged forty-four. Admitted to University of California Hospital August, 1920 complaining of difficulty in walking, backache, and numbness of the lower extremities.

Family history revealed a suspected luetic infection in the patient's husband. She had typhoid at fourteen years of age and influenza at forty-three. At the age of twenty-three she had an operation for suspension of the uterus. The present complaint dates from a fall two years before admission. On examination the essential findings were spastic gait; absence of abdominal reflexes; hyperactivity of deep reflexes of the lower extremities, and bilateral Babinski. Both feet were

hyperesthetic. Urine was negative. Blood-count showed Hb., 78 per cent.; R. B. C., 3,400,000; W. B. C., 7600, and differential count within normal limits. Later in the observations of the case mental symptoms occurred largely characterized by emotional instability. By October the patient had grown extremely nervous and the mental symptoms were more marked, and she complained of lancinating pains in the lower extremities and loss of sphincter control. Spinal fluid examination showed negative Wassermann; positive globulin and a paretic gold curve.

Anatomic diagnosis was chronic endocarditis; chronic adhesive pleurisy; chronic peritoneal adhesions, and a degenerative lesion of the cord.

Neuropathologic study revealed a marked subacute myelinic degeneration of the posterior columns. In the degenerated areas several large vessels showed lymphocytic infiltrations around them. The meninges showed lymphocytes and occasional plasma-cells. Cortical sections revealed perivascular softening.

This case presented difficulties in diagnosis. While combined system disease was considered because of the neurologic findings associated with an anemia, the luetic history, together with a paretic gold curve, suggested paresis, particularly as the patient developed definite mental symptoms. In this connection it is to be pointed out that a frank diagnosis of paresis without positive Wassermann findings cannot be justified. A brain tumor without localized signs was thought of, but against this diagnosis was the absence of signs of intracranial pressure. Finally, gynecologic examination presumably revealed a pelvic tumor, which it was thought could account for the back pains and some of the neurologic signs, but could not account for the mental symptoms except on a basis of psychosis associated with the anemia or a brain metastasis. There were so many conflicting elements in the case that a diagnosis of combined system disease could hardly be justified.

Case I presents the usual picture of combined system disease with subjective paresthesias, usually of the "stocking and glove"

type, and general weakness. Objectively, the extremities are spastic with exaggerated reflexes. Some cases show first a spastic paraplegia which is followed later in the disease by a flaccidity, abolition of deep reflexes, and positive Babinski. In the later stages a muscular atrophy frequently follows as a result of destruction of ventral horn cells. Cases frequently conform to the type described by Gowers as ataxic paraplegia. While the blood-picture may at first be within normal limits, in most cases it assumes the characters of a grave anemia later in the disease. Woltmann found that 33 per cent. of cases which showed combined sclerosis presented pictures of pernicious anemia at some time during their clinical course, while 80.6 per cent. of cases of pernicious anemia showed destructive lesions in the central nervous system.

Case II suggests the difficulties in diagnosis of cases of combined system disease, and emphasizes the fact that this condition often presents a problem in clinical diagnosis. In cases in which anemia exists, with neurologic signs and symptoms, this disease should be considered. There should be little difficulty in differentiating combined sclerosis from multiple sclerosis in the presence of anemia and paresthesias and absence of cranial nerve involvement, early sphincter trouble, and intention tremor. Ataxia and alterations in reflexes may lead to confusion with tabes dorsalis, but combined system disease rarely shows Argyll-Robertson pupils and the sensory disturbances typical of tabes. Serologic examinations are valuable diagnostic aids in differentiating between the two conditions. Other conditions to be differentiated are Friedreich's disease, amyotrophic lateral sclerosis, myelitis, spinal cord tumors, and multiple neuritis.

Neuropathologic findings in combined system disease are constant in the cord, consisting of a subacute myelinic degeneration of the dorsal and lateral columns, with an older process in the form of axis-cylinder degeneration. Cortical sections from many cases show degenerative foci, often in the vicinity of vessels; with shrinking, vacuolization, and tigrolysis of nerve-cells. The pons is usually free from pathologic changes. Rarely there are to be found ventral horn cell changes as in Case I,

and degenerative myelinic alterations in the spinal ganglia and spinal nerve roots. A frequent finding is the presence of lymphocytic perivascular infiltrations in the cortex and cord as evidence of the possible toxic nature of the destructive process. Clinicians should bear in mind the necessity of neurologic study of cases with grave anemias, and search out toxic foci. Cases of combined system disease are overlooked in which central nervous system pathology is prevalent. While the nature of the toxins producing degenerative changes is unknown, it is probable that the anemias and accompanying scleroses are due to the same causes.

CLINIC OF DR. HIRAM E. MILLER

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RECENT EXPERIENCES IN THE TREATMENT OF LEPROSY

IN a recent article,[1] the unsatisfactory results obtained in the treatment of 21 cases of leprosy at the San Francisco Hospital were reported. They had been given intramuscular injections of the ethyl and butyl esters of the total fatty acids of chaulmoogra oil. The lack of improvement was thought to be due to: (1) the advanced age of many of the patients; (2) the long duration and severity of the disease in most of them, and (3) the surroundings in which they were forced to live. The report was almost entirely discouraging.

In this paper I will discuss the type of case in which the outlook is more encouraging and hopeful. Two cases of maculo-anesthetic leprosy will be presented which have shown considerable improvement and in whom I hope in time to see the disease arrested.

Case I.—C. A. E., forty-seven years of age. Duration of symptoms six months. American, born in Ohio, who spent one year in Brazil when twenty-one years of age. With this exception, he had never been outside the United States. Physical examination was negative except for a palm-sized, slightly erythematous, crenated, macular area with a definite border just above the left internal malleolus. Entire area was anesthetic to pin-prick. It was difficult for the patient to distinguish heat from cold in the area. Skin and mucous membranes otherwise

[1] Experience with Chaulmoogra Oil Derivatives in Treatment of Leprosy, by Morrow, Walker, and Miller, Jour. Amer. Med. Assoc., vol. 79, No. 6, August 5, 1922, p. 434.

normal. Smears from nostrils were negative for lepra bacilli. Microscopic examination of a biopsy taken from the border of the lesion showed the following findings. The epidermis was thinned, the corium contained areas of rather dense round-cell infiltration in which there were a few vacuolated cells (Virchow's cells). The areas were arranged in a cuff-like formation around the blood-vessels and coil glands. Lepra bacilli were not demonstrated in the sections. The Wassermann reaction was triple plus in the blood-serum. The patient denied luetic infection. He had been given five neosalvarsans and twelve mercury salicylate injections by his family physician without clinical or serologic improvement. He was started on intragluteal injections of 2 c.c. of the ethyl esters of the total fatty acids of chaulmoogra oil twice a week. Five months later it would have been impossible to make a clinical diagnosis of leprosy. The lesion had almost entirely cleared, but the anesthetic area could still be outlined with a pin-point.

Within the next few months the patient began to complain of pain at the site of injection, dull pains in all the joints, and severe general malaise. These are toxic symptoms which I have learned to look upon as due to continued saturation of a sensitive patient with chaulmoogra oil. They are very severe and even a stoical patient may complain bitterly of them. Treatments were discontinued for a period of two months. During this time the area on the lower leg became more prominent and the patient developed an erythematous, anesthetic, macular area with a raised border on the upper lip and extending over on to the right cheek.

After this rest period the patient was given 3 c.c. of the butyl esters of chaulmoogra oil at weekly intervals. It had been found that this ester was much better tolerated by the patient than the ethyl esters and that it had the same therapeutic value.

The patient has received the ethyl esters for a period of seven months and the butyl esters for five months. The area on the leg is markedly improved; there is only a faint crenation of the skin remaining over the site of the lesion. The sensation

has not returned. The areas on the face are still slightly erythematous, but no longer palpable. There is no appreciable loss of sensation over this area. The general health of the patient is excellent.

Case II.—F. R. M., forty-five years of age. A British subject, born in Australia. Duration of symptoms one year. The patient had lived in Australia for the last two years and the nine preceding years had been spent in South Africa. Physical examination revealed the following positive findings. There was a slightly raised, erythematous, walnut-sized area with a definite border on the left side of the chin. There was a similar but larger area anterior to the left ear and extending around behind it. Over the left lumbar region was a macular erythematous, slightly crenated area about the size of two palms, with a raised border and somewhat paler center. There was a chicken-egg-sized area on the right anterior wrist that formed a complete ring. It had a broad raised border and clearing center. The ulnar nerves were not noticeably enlarged. There was no atrophy in the ulnar nerve distribution, but the patient stated that this area felt "dead and putty-like." There was almost complete anesthesia to pin-prick in all the macular areas. The patient was unable to distinguish heat from cold in any of them. Sensation elsewhere was normal. Smears from the nostrils were negative for lepra bacilli. Material from deep in the border of the lesions on the face and back failed to reveal the bacilli. Microscopic examination of a biopsy taken from the border of the lesion on the back showed the following findings: The epidermis was normal. There were scattered areas of round-cell infiltration in the corium. This infiltration was arranged around the blood-vessels, hair-follicles, and sebaceous glands. In one section two giant-cells were seen. There were a few vacuolated cells in the midst of the round-cell infiltration. Lepra bacilli were not demonstrated in the sections.

The clinical picture was complicated by a cerebrospinal lues with Argyll-Robertson pupils, absent knee-jerks, and paralysis of the tibialis anticus muscle on the right. The Was-

sermann in the cerebrospinal fluid was double plus. The blood Wassermann was triple plus in two antigens.

When the patient presented himself for examination he had a generalized dermatitis of moderate severity following the injection of ten salvarsans. These had been given in Honolulu and the Orient, with the idea that all of his signs and symptoms were of a luetic nature. The dermatitis cleared within six weeks under the application of soothing lotions.

This patient has received weekly injections of 3½ c.c. of the propyl esters of chaulmoogra oil for a period of eight months. The improvement in the first two months was rapid. The areas on the right hand and back became of a light brown color and the palpable border entirely disappeared. There was very little return of sensation. The areas on the face were of more recent development and responded more slowly to treatment. At the present time all areas are of a light brown color and are no longer palpable. The pigmentation in the area on the back is fading and not much more than the border of it can be seen. The sensation in all areas is about the same as when first examined. However, the patient states that the "dead and putty-like" feeling in the right wrist and palm have disappeared and the areas now "feel alive." The general health of the patient is excellent.

These 2 early cases of maculo-anesthetic leprosy will serve to illustrate a type of the disease in which chaulmoogra oil derivatives are of great value. In early nodular cases the improvement may be even more rapid and striking.

Leprosy has not been treated for a sufficient period of time to have any established criteria of cure. However, I think one may consider the disease as arrested when (1) the active lesions have disappeared or have become small and fibrous; (2) lepra bacilli are not found in the nostrils, nodules, or macules where they were formerly numerous; (3) the patient has received two years of treatment after the disappearance of all lesions and lepra bacilli.

The blood Wassermann is positive in most cases of leprosy perhaps more often than in late syphilis. I have not had the

opportunity to follow the effect of chaulmoogra oil treatment upon this reaction in any arrested cases, nor have I seen any reports upon the serologic findings in arrested cases in the Hawaiian Islands, India, or elsewhere. This may be an additional criterion of cure.

These 2 cases which I have reported will be treated until clinically well, and then weekly injections will be given for an additional two-year period. If they remain free from symptoms during this time I will feel that the disease has been arrested and perhaps cured.

CLINIC OF DR. LAURENCE R. TAUSSIG

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THE RADIUM TREATMENT OF CARCINOMA OF THE MOUTH

THE radium treatment of malignancy is a relatively new science, and the method of application has been changed so much that it is not yet possible to judge correctly its value in comparison with other methods which have been in use for a longer period. All who have had experience with this agent have seen malignant conditions, considered hopeless, melt away like magic under radiotherapy. On the other hand, cases are seen which are regarded as having a relatively good prognosis in which treatment is unavailing, and in some cases it apparently increases the rate of growth. This is also true for other methods of treating malignancy. At the present time the large portion of the patients referred for radium therapy are the hopeless ones who have either been treated unsuccessfully by surgery or have deferred seeking expert advice until the time for the possibility of cure has passed. In spite of this, the number of satisfactory results has been encouraging; and we will soon be able to recognize certain types of malignancy for which radiotherapy, either alone or in combination with surgery, is the treatment of choice. Many are inclined to include carcinomas of the buccal cavity in this category.

Three cases will be demonstrated to illustrate types of mouth malignancy suitable for radium therapy and to indicate the technic and progress under radiotherapy.

The first patient is a relatively young man of forty, who enters the clinic for treatment of an ulcer of the tongue. He has known of the existence of the lesion for about four months, and has been treated for the past two months with "electricity"

by a charlatan. The lesion (Fig. 89) is a fissure-like ulceration in a hard, nodular mass on the right side of the tongue, extending from just in front of the anterior pillar to within about 4 cm. of the tip of the tongue, and the palpable induration extends well over the midline. There are no palpable cervical glands. The condition is clinically carcinoma, but in every case of this type it is very important to rule out lues. There is no history of infection and the marital history is negative as regards any indication of syphilis. There is no gland enlargement or other sign of lues. In addition, the Wassermann reaction is negative. The location is that of carcinoma rather than of gumma, and the cartilaginous consistency is in favor of malignancy. These facts are sufficient to rule out a specific lesion. The disfavor in which biopsy is held by a large number of authorities influences us to reserve it for the more doubtful case. However, I do not believe that there is any authentic evidence that damage is done by a properly performed biopsy in this type of case. The only surgical procedure which would have the least chance of curing this patient would be a complete amputation of the tongue, with the removal of the entire floor of the mouth. The primary mortality of the operation would be exceedingly high and the chance of cure small. The lesion is too extensive to consider using the actual cautery. The application of radium to the surface would possibly cause a temporary improvement, but experience has proved that the result would be merely to heal over the surface. The treatment of choice in this type of case is the insertion of unscreened tubes of radium emanation. These tubes are about 3 mm. long and 0.3 mm. in diameter, with smooth ends, to produce the least possible traumatic irritation. Each tube contains from 1 to 1½ millicuries of emanation, and they should be distributed so that there is one to each cubic centimeter of tumor. These so-called "bare tubes" should be inserted into the malignant tissue itself rather than into the surrounding normal tissue. It is often difficult to tell accurately how deep the cancerous involvement extends, and it is better in such a case to err on the side of burying the tubes too deeply rather than to leave any of the carcinoma unradiated. The

point of superiority of this method of treatment is in the even and intense radiation of the entire growth at one time.

Bagg, of the Memorial Hospital of New York, has shown that the destructive action of radiation from bare tubes extends about ½ cm. in all directions from the tube, so that if we have seeded the mass evenly with one tube per cubic centimeter, we will get a complete destruction of the primary lesion. He

Fig. 89.—Carcinoma of the tongue.

further demonstrated that the extent of the action was very nearly the same for a tube containing 1 millicurie as for one containing 5 millicuries. That is the reason we prefer to use tubes averaging between 1 and 1½ millicuries. For this case we will use 9 tubes containing a total of 11.2 millicuries of emanation. The tongue should be infiltrated with 2 or 3 c.c. of ¼ per cent. novocain solution. Each tube is loaded into the lumen

of a needle especially designed for the purpose, the needle is thrust into the desired spot, and the stilet, which extends flush with the point of the needle, is pushed out, depositing the tube in its place. If the tissue to be radiated is rather fibrous, the

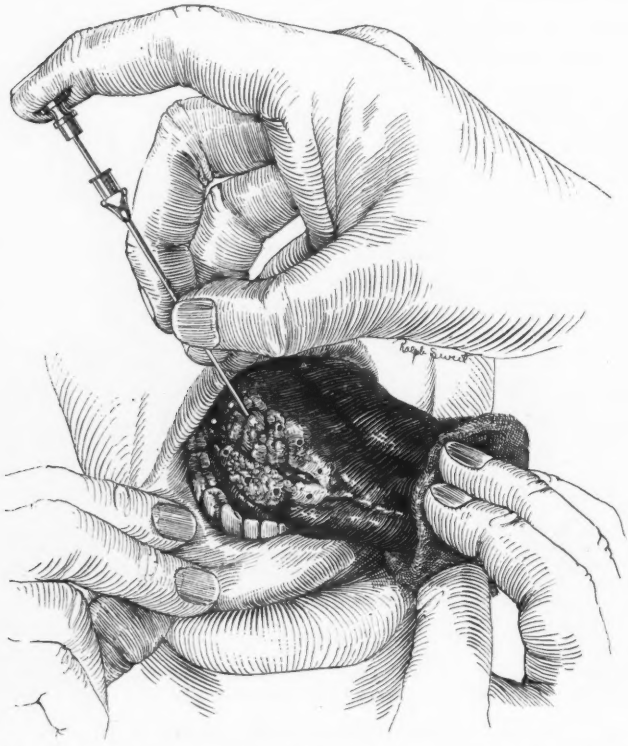

Fig. 90.—Method of implanting "bare tubes" of emanation in carcinoma of the tongue. The dots indicate the sites of other punctures.

needle should be withdrawn ½ cm. before thrusting home the stilet. Figure 90 illustrates the method of inserting the emanation, the dots indicating the sites of the other punctures. Following the treatment the patient will have a little pain due to the needling after the anesthetic effect of the novocain wears off.

This will not last long. In about a week, however, the true reaction will commence. This consists of a burning pain in the tongue with swelling. Following this a slough will develop which takes a variable time to come away. Late in the reaction there is apt to be considerable neuralgic pain, frequently extending up to the ear. The period and intensity of the reaction is variable. Some of the patients keep up their work and complain very little. Others are very sick. During the period of reaction cleanliness is essential. The patient is given a mild alkaline mouth-wash and instructed to rinse his mouth every hour or two with warm solution if practicable. He is kept under close observation if possible and appropriate narcotics are prescribed when necessary. Whether there are palpable lymph-nodes or not, it is advisable to give the cervical region a thorough course of *x*-ray therapy in the hope of sealing off the lymphatics. It is probable that the *x*-ray in this field is just as efficient as a radium pack, though the latter may be used if it is convenient. The main point is thorough radiation of the neck. Should metastatic glands develop during treatment, it is advisable to remove them surgically if possible, continuing the radiation subsequently; or, if they are not operable, bare tubes of emanation may be inserted into them. The technic is the same as for the treatment of the primary lesion and the dose is calculated in the same way. It does not seem logical nor has it been proved useful to do a block dissection of the neck glands in every case regardless of the clinical condition.

The next case is one of a man who comes in for observation. He was first seen one year ago, when he entered with a tumor of the inner surface of his left cheek. The lesion itself was about 6 cm. in diameter and 1½ cm. high. It was nodular, hard, and with but little induration of the cheek wall. He had had it for three or four months. He is an upholstery worker and holds a mouthful of tacks most of the working day. The tongue presented a glossitis of the geographic variety, suggestive of lues. There were no palpable glands. The Wassermann was negative. Five bare tubes, totalling 9.5 millicuries,

were inserted into the mass, and the patient was sent for prophylactic *x*-radiation of his neck. On account of the suggestive condition of the tongue, mixed treatment was given for a time under the impression that the carcinoma might have developed on a luetic base. It had, however, no effect on the condition of the tongue. Within a month the reaction had subsided and the mass had entirely receded. There was a small cavity in the cheek as a result of the treatment and some thickening around it, probably scar tissue. Two months after treatment he had a severe hemorrhage, which was controlled by local means, without resorting to ligation. Six months after treatment was instituted we became convinced that the area of thickening was increasing. The question as to whether such a condition is merely scar tissue or whether it is a recurrence is one of the most difficult to answer in many instances. One does not feel justified in incising the mass for diagnostic section, neither does one like to let it go until the clinical picture is unmistakable and the time for curing is past. Furthermore, one hesitates to cause the patient the discomfort and expense of further treatment. In this case, however, we decided on more treatment, and inserted 4 bare tubes, totalling 2.4 millicuries, into the suspicious mass. This moderate dose caused very little reaction and a rapid disappearance of the mass. This would have been the case whether it was scar tissue or malignant, so we are still in the dark as to what the process represented. Five months ago he developed a hard nodule at the tip of the tongue, apparently a carcinoma. We inserted 2 bare tubes, totalling 1 millicurie, into the mass. This caused a severe reaction, with much pain. The tongue is still tender and there is still an indolent ulceration at the tip which is gradually healing. There is still some slight induration in it which is probably scar tissue. The tip of the tongue is somewhat limited in its movements by the scarring about it. In the cheek can be felt a small smooth scar. There are no palpable glands. This is one of the cases that has primarily responded well to radiotherapy, but whether the cure is permanent or not will not be known for several years.

The last case is that of a man who came in with a nodular, ulcerative, hard lesion of the posterior edge of the soft palate, involving the left side of the uvula. He had received a course of antiluetic therapy in spite of a negative blood Wassermann, and it had no effect on the growth. Four bare tubes, totalling 3.8 millicuries, were inserted into the growth. The reaction was quite severe, but had practically cleared one month later, at which time everything was soft except for the left side of the uvula, which felt as though it might be carcinomatous. To be on the safe side 1 bare tube of 1 millicurie was inserted into the mass. It is now just a week since this last treatment, and there is a yellowish-white slough at the site of the last bare tube and an erythematous area about it. The whole thing feels soft and smooth. The patient has been having a good deal of pain the last day or two, especially in eating. The cervical region received a course of *x*-ray therapy soon after the first bare tube treatment, and there have been no palpable lymph-nodes.

The first case demonstrates one method of handling mouth cancers. The last two show some of the difficulties encountered, even in the cases that respond well primarily to radiation. The problem of properly judging the initial dose is one of great importance, and will only be solved by much clinical experience. It is probable that an average dosage of 1 millicurie per cubic centimeter of tumor is efficient in most cases, but the estimation of the volume is rendered difficult by many factors. Furthermore, there is a marked variation in the radiosensitiveness of malignant tumors, even in those clinically and pathologically identical so far as we can tell. As a rule, the radium treatment should not be kept up unless the patient shows prompt and definite improvement. It is often very hard to say whether another treatment should be given, and if so, when. Scar tissue is usually smoother and softer than new cancerous tissue, but one can easily be misled.

The use of intratumoral radiation, either by "bare tubes" or by steel needles containing radium, gives us the best method of treating carcinoma of the buccal cavity, though the results are still far from ideal.

CLINIC OF DRS. ALFRED C. REED AND
HARRY A. WYCKOFF

STANFORD UNIVERSITY HOSPITAL

INTESTINAL PROTOZOA IN CLINICAL PRACTICE[1]

WE wish to present for your consideration a group of cases harboring intestinal protozoa. No other basis of selection is adopted than this. These cases are derived from the medical clinic ward service and from private practice. Not all such cases will be presented, but only enough to illustrate the frequent occurrence of intestinal protozoa in general practice and to emphasize the wide-spread medical neglect of this group.

It has been the experience in California that increasing accuracy of diagnosis and more frequent search for protozoa are rewarded by a constantly increasing number of cases in which protozoa are found present and associated directly with the patient's symptoms. Amebas, flagellates, and to some extent ciliates are evidently of wide occurrence in this State, and doubtless will be found much more freely distributed over the entire United States than has thus far ever been suspected. In California the sources of the present endemic distribution are as follows:

1. Immigration from the Orient, especially the Filipinos, Chinese, Japanese, and East Indians.
2. Immigration and transient labor from Mexico.
3. Tourist travel from California to Asia.
4. The army demobilization.
5. Trade routes centering in California ports.

Much remains to be learned of the specific pathogenicity of intestinal protozoa for man. It is known that the human

[1] From the Department of Medicine, Stanford University Medical School.

intestinal tract is inhabited by an extensive bacterial flora which, in general, is useful in the economy of digestion, or, at worst, is not harmful to it. So it has been said by way of analogy that it is possible to have a protozoal fauna consisting of neutral commensals quite without ill effect on the host. It is conceded that outside of this relatively large group of benign protozoa there is a hostile minority whose presence always bespeaks danger. This relationship is said to be analogous to that between the normal intestinal bacteria and such evil invaders as, for example, cholera or typhoid. But the analogy is fallacious. The normal bacteria of the human intestine have a definite physiologic function and serve a useful and necessary purpose. No such benefits have been proved or even suggested as attending the presence of any protozoa whatsoever. Moreover, it has yet to be proved in most cases that protozoa can exist in the intestinal canal without damage to its walls, without liberating any toxin, without causing any irritation or stimulation, or without ill effect on the chemistry of the intestinal contents.

While we are willing to concede that protozoa may inhabit the intestine without producing clinical symptoms, we are not yet ready to affirm that any protozoa can exist in the intestine without increasing the likelihood of disease in the host. We believe that all protozoa are dangerous potentially if not directly. We believe that almost invariably the presence of protozoa can be related to pathologic factors of some sort present in the host. Closer study may well demonstrate results of protozoal action of which we are now ignorant. Potentially, danger may be relative to the mass of invading organisms. This occurs in a sense in amebiasis. Here it is understood that with a small mass of infection even a strongly pathogenic organism may cause no more than local or latent damage and produce no symptoms. Potentially, too, danger may be relative to temporary, local, or general lowering of resistance on the part of the host. We see previously harmless bacteria suddenly become virulent, as in the case of the onset of acute symptoms in a healthy cholera carrier exposed to chilling, fatigue, or an intercurrent digestive upset. Such a condition was demonstrated

experimentally in the case of amebic infection by McCarrison in India. McCarrison worked with monkeys which were carriers of Entamœba histolytica. No symptoms appeared until the onset of dysentery in the presence of a vitamin deprivation.

With such considerations in mind it seems logical to assume that all protozoal intestinal parasites are potentially pathogenic. Some are relatively harmless. None are safe. All jeopardize the health of the host.

At best it is notoriously difficult to relate specific symptoms to specific causes. Nowhere is this difficulty more marked than in protozoal bowel infestations. Given a symptom plus a protozoan parasite, we remove the parasite and the symptom disappears. Too often we hastily assume that the parasite had caused the symptom. Or the symptom does not disappear, and we erroneously conclude it was not caused by the parasite. We cannot always draw a final judgment from clinical observation alone. Until our judgment is perfected, therefore, we can safely consider that the patient's best good lies in eradication of the parasite.

All clinical symptoms arising from the presence of protozoa in the intestine must result in accord with one or more of the following mechanisms:

1. The effect of local pathologic changes in the intestine or other tissues directly invaded.

2. Absorption of protozoal toxins of a more or less hypothetic nature.

3. The absorption through protozoal lesions of parenteral protein or bacterial products. This is probably the explanation for the inflammatory reaction and enlargement of lymphatic glands draining areas of amebic invasion.

4. Reflex effects resulting from the presence of protozoa in the colon or elsewhere. If an inflamed appendix can be responsible for reflex constipation or gastric symptoms, it is equally conceivable that a protozoal lesion can cause intestinal and digestive disturbances through a reflex mechanism.

Let us take up in detail some cases of protozoal infection. We will consider first:

BALANTIDIUM COLI[1]

Roughly resembling an American football in shape, this relatively large protozoan consists of an outer coating or ectoplasm, covered with fine cilia. Near its somewhat smaller anterior end is the mouth, which opens in a rather indefinite way into the endoplasm. Lying within the endoplasm is a roughly reniform nucleus appearing to have a more or less distinct smaller portion connected with it, sometimes called the micro-

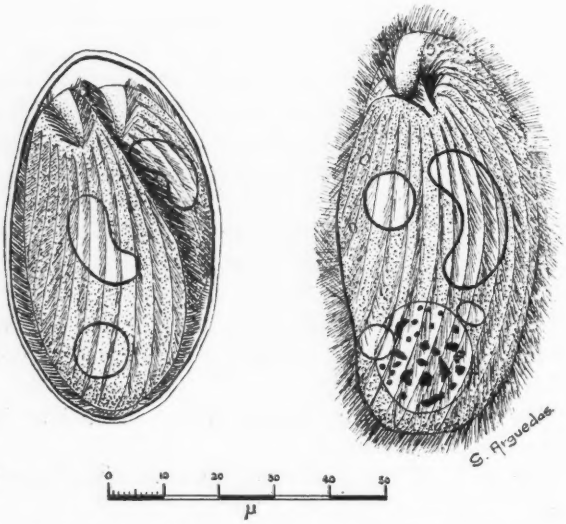

Fig. 91.—Balantidium coli, encysted and free (after Wenyon).

nucleus. The organism possesses, also within the endoplasm, two contractile vacuoles which must be distinguished from the temporarily produced vacuole-like spaces forming within the substance of the endoplasm about ingested food particles. The cysts are spheric or oval.

Infection probably depends upon the presence of these cysts in human feces and in the feces of hogs. In that animal it is a

[1] With the exception of Balantidium, these illustrations represent camera lucida studies.

common and seemingly harmless parasite. There is small doubt that man acquires the infection as a result of close association with infected hogs.

Balantidium infection is comparatively rare in man if we may judge by the number of reported cases which scarcely exceed 200 to date. This parasite inhabits the large intestine and is rather indolent in its clinical development. When the customary alternation of constipation and diarrhea is present, its lesions consist of ulcerations involving the mucosa and submucosa. These ulcerations are apt to be aggravated by secondary bacterial invasions. Ulceration and abscesses of the colonic wall are produced, however, by the balantidium alone. The parasite is very infrequent in the United States.

Case I.—W. S. A five-year-old boy whose general history was excellent, except for a tendency to constipation. He began to complain of colicky pain in the abdomen and the bowels were costive. When seen some five days after onset he had deep, definite tenderness in the right lower quadrant and an indefinite sausage-shaped mass. Blood-count showed 45,000 white cells, with 85 per cent. polynuclears, 7 per cent. lymphocytes, and 8 per cent. mononuclears. There were no eosinophils seen. The stool showed a normal digestive result, no ova, no amebas, but huge numbers of Balantidia coli. Examination of the stools of the parents and one brother revealed no parasites. The patient had been raised in the city and no source of infection could be traced. Dr. Langley Porter saw the boy and concurred in the diagnosis of acute appendicitis. Operation was refused and a slow recovery took place. In two years there has been no recurrence and no gastro-intestinal symptoms other than occasional constipation.

The case here presented can remain simply as an instance of acute appendicitis associated with the presence of balantidia in the stools. There was no previous significant history. There was no earlier association or contact with pigs. Operation was refused, the patient regained normal health, and has kept it for the last two years. It is impossible to say definitely that the

balantidium was responsible for the inflamed appendix. It certainly is not possible to say that the balantidium was harmless in this respect.

We will next present very briefly a single case of infection with

CHILOMASTRIX MESNILI
(Macrostoma Mesnili)

In shape this flagellate resembles an elongated top. There are three active flagella projecting from the blunt end.

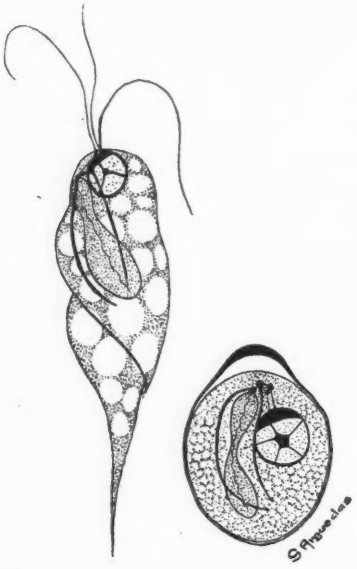

Fig. 92.—Chilomastrix mesnili. Vegetative and encysted forms.

Seen in the stool its more remarkable characteristics are its rather active progression, accompanied by rotation about the long axis; a prominent longitudinal slit on one surface, in the floor of which is the mouth; a usually well-defined spiral groove running about the body from mouth to tail, and, sometimes, its spotted cytoplasm.

The organism forms small oval cysts with a blister-like prominence at one end. In stained specimens the remains of the mouth groove may be seen, and to one side of this a less evident globular nucleus. Cysts probably remain viable for some time in moist feces, thus providing a source of infection.

Case II.—A. A. G. A man of sixty-four years, a retired rancher, had suffered for two years from a classical picture of pernicious anemia. He had been under the care of various competent internists. His condition had been exhaustively investigated and no etiologic factor discovered. He underwent several transfusions of blood, with the usual temporary remissions. A few days previous to the onset of the pulmonary infarction, which resulted in his death, examination of the stools showed a massive chilomastrix infection. This may well have been an accidental finding with no significance relative to the anemia. One could wish, however, that this angle of the case had been adequately studied at a much earlier date.

The following cases illustrate infection with

TRICHOMONAS INTESTINALIS
(Trichomonas Hominis)

A very active organism in fresh stools, it is variable in shape, but generally rather ovoid, the smaller posterior end provided with a slightly curbed spike. There are three or four rapidly lashing flagella at the rounded anterior end and a prominent undulating membrane extends along practically one whole side.

Considerable difference of opinion exists regarding cyst formation by this organism, but it seems reasonable to assume that infection occurs by ingestion of cysts as in the other flagellates.

Case III.—Mrs. F. W. N., a woman of fifty years. This patient has suffered all her adult life from spells of nausea and vomiting. For the past nine months she has had a nearly constant diarrhea associated with achylia and only relieved temporarily from time to time by acid mixtures. She has not seen blood in the movements nor has she suffered pain. She has

a considerable secondary anemia. She has lost 30 pounds in weight. Examination reveals a highly nervous and neurotic woman in poor nutrition, but with no objective abnormality. The stools show a trichomonas infection. The striking and remarkable feature of this case is the appearance in the gastro-intestinal *x*-ray plates of tumors in the wall of the stomach and midportion of the transverse colon which we believe are

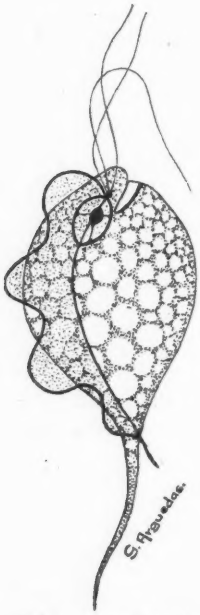

Fig. 93.—Trichomonas intestinalis (adult).

adenomatous papillomas. This lesion is extremely rare, and at a future time a full case report will be presented of this unusual condition. From the present point of view it can be said with safety that the trichomonas undoubtedly increased the irritability of the digestive tube and undoubtedly has intensified the symptoms. It is unlikely that trichomonas has any causal relation with the tumors, and their co-existence is, without doubt, purely accidental.

Case IV.—B. D. This patient is a man of sixty-three years with a long and involved history. He was under close observation in the medical ward, where the following diagnosis was established:

1. Paranoia of expansive type.
2. Old anterior poliomyelitis affecting right arm and both legs.
3. General arteriosclerosis, with extensive vascular calcification, especially involving the brain. Hypertension averaging, while at rest in bed, 212/100.
4. Myocarditis and hypertrophy of heart.
5. Extensive Type II arthritis of spine and left ankle.
6. Intestinal infection with Trichomonas hominis.

Spinal fluid and Wassermann are normal. Blood-count is normal.

The patient is a native of the United States and has spent his life chiefly in the northern part of this country, largely in New York. He has traveled abroad extensively and served through the Spanish-American War, in which he was slightly wounded.

One year ago he had an attack of severe epigastric pain with nausea and vomiting which required morphin for relief. This disappeared entirely in the course of a few weeks, leaving him with gaseous eructations only. Again three months later he suffered from a similar attack which persisted for five weeks. A third attack came on five days ago. *x*-Ray studies showed evidence of adhesions involving the distal half of the stomach and also adhesions in the right flank involving the ileum and colon. There was no evidence of colitis or ulceration. Fractional testing of the stomach contents showed a constant hyperacidity.

The discussion of possible relationships between hypertrophic or Type II osteo-arthritis and protozoal infection will be deferred to a later section. Suffice it now to note that the trichomonas infection is associated with the gastro-intestinal history and findings just described, and also with an extensive Type II osteo-arthritis.

We turn now to the most frequent and most dangerous of the flagellates,

GIARDIA INTESTINALIS
(Lamblia)

In appearance giardia is probably the most grotesque of the intestinal flagellates.

Fig-like in shape when viewed in its broad dimension, it has on the ventral surface of its larger anterior end a circumscribed area with raised edges, the "sucking disk." Within the disk

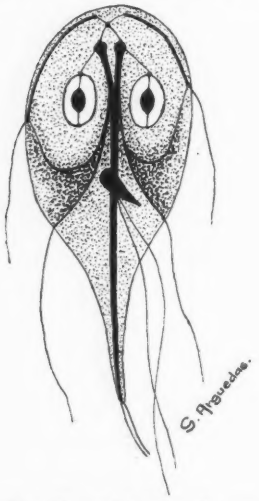

Fig. 94.—Giardia intestinalis, motile form.

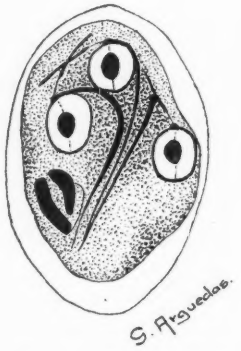

Fig. 95.—Giardia intestinalis, encysted form.

and appearing to lie just dorsal to its floor are two nuclei, symmetrically placed on either side of the midline. There are four pairs of flagella, three appearing to emerge from each side of the organism and a pair trailing from the small posterior extremity. In lateral view giardia roughly resembles an old-fashioned, curved ear-trumpet, its smaller posterior portion or tail curved dorsally, the sucking disk presenting ventrally. In the stools, giardia appears to bob about briskly, but without true progress in any direction. The organism lives in the

upper part of the small intestine and probably attaches itself by means of its sucking disk to the mucous membrane.

But far more often than the active flagellates, cysts are seen in the stool. Examined in iodin solution, giardia cysts appear as small, oval, sharply outlined bodies with a rather complicated and minute inner structure. Cysts survive for a time in moist stools. Stiles has brought forward evidence which points strongly to the house-fly as one factor in the dissemination of these cysts.

Giardia is of common occurrence in California, and while its pathogenicity has been disputed, it is impossible to believe that it is a harmless or safe parasite under any circumstances. The following cases are selected as typical of the clinical associations of this parasite. They illustrate its unsuspected frequency as well as the clinical improvement with removal of the flagellate. The treatment of flagellates is extremely unsatisfactory in general. To shorten a long tale of therapeutic recommendations and failures, it may be said that we have met with best success in the treatment of giardia by using the same general scheme as in the treatment of amebiasis, adding two moderate courses of thymol by mouth. Neosalvarsan alone does not cure. Not infrequently giardia cysts reappear after any form of treatment, but we have been successful in curing a number of cases in two months by the method indicated.

Case V.—W. S. C., a male lawyer, aged thirty-four, has been under treatment in various places for neurologic symptoms. His father is a diabetic. Previous to tonsillectomy two years ago the patient had several attacks of rheumatism of the large joints. Five years ago was treated for hookworm infection. Seven years ago he had a severe diarrhea, with no blood or mucus in the dejecta, and without much pain, that lasted for six months. For the next three years he had at times mild attacks of a similar diarrhea. He has fixed pupils which have been diagnosed as of the Argyll-Robertson type. They contract, however, under eserin. Patient has spent most of his life in the Sacramento Valley and bay district.

His status, when first seen, had been considered neurologic and suspicious of tabes. He complained of great weakness, various phobias, unsteadiness on his feet, nervousness, depression, and severe palpitation and breathlessness on exertion. His habits were good. He suffered from emotional upsets and had frequent heavy sweats. Previous to this for seven years he had constantly been in poor health even when free from the symptoms which now bother him. At times his wind is good and he can undertake considerable physical exertion. In spite of repeated negative blood Wassermanns and a negative venereal history, he has been told and he believes that he has tabes or some other equally serious nervous disease, also that his heart is in a bad way.

Examination shows a compact, well-built young man, fairly well nourished. He is obviously intelligent, educated, and reasonable in his point of view. He has no gland enlargement, the thyroid is palpable, the skin is clear, reflexes are normal or exaggerated. The eyes do not accommodate or react to light. The fundi are normal. His lungs are clear.

His heart shows an increase of 1 inch in transverse diameter; the pulse-rate is between 72 and 120; there are no murmurs. Blood-pressure, sitting, auscultatory, Mercer instrument, is 120/72. Reaction to standard exercise is entirely normal. Abdomen shows no abnormality.

Laboratory findings are as follows: Basal metabolism $2\frac{1}{2}$ per cent. plus. Spinal fluid is normal in pressure, cells, globulins and sugar, and gives negative Wassermann in all dilutions. Blood Wassermann is negative. Blood-count: White cells, 6450. Polynuclears, 66 per cent.; lymphocytes, 25 per cent.; mononuclears, 1 per cent.; basophils, 1 per cent., and transitionals, 7 per cent. Red cells, 4,400,000, with 75 per cent. (Sahli) hemoglobin. Urine is normal. Temperature and respiration are normal.

The stool shows an extremely heavy giardia infection. Diagnosis: Neurasthenia. Irritable heart. Giardia infection. Treatment was kept up for six weeks, resulting in a cure of the parasitism and the complete disappearance of all symptoms. Today he

feels and looks in excellent health. Such definite and extensive clinical improvement following immediately on removal of the protozoa offers a striking substantiation of the belief already expressed, namely, that protozoa may cause reflex and indirect, as well as direct, symptoms.

Case VI.—D. B. R. This young man of twenty-four years has had stomach trouble for two years past. He has had no other symptoms. At night and about two hours after eating he has a dull boring pain in the epigastrium. He has been troubled constantly with flatulence and constipation. He has had no nausea or vomiting until the past week, during which he has vomited several times, with relief from the pain. The pain is relieved by eating. His father died of ulcer of the stomach and the patient fears a similar outcome for himself.

Examination shows no significant abnormality except epigastric tenderness and deep tenderness in right lower quadrant. He has a moderate secondary anemia. Otherwise his status is normal. The stools show giardia infection and cysts of Entamœba histolytica. At the present time he has nearly completed his treatment for these parasites. The stools are negative. His pain has completely disappeared and his bowels are regular. He has had no dietary instructions and treatment has been limited to eradication of the parasites.

It cannot be said yet that he is cured. Our criterion of cure is three months' freedom from parasites following treatment. Examination for parasites means for us the critical and intensive search of at least six stool specimens collected on successive days. In the course of these six analyses one treatment with Epsom salts is given.

Case VII.—P. McK., a mechanic, aged thirty-nine years, who has had what he calls a "weak stomach" for twenty years past. He says that tiring, the slightest overeating, or any indiscretion in diet causes severe nausea and vomiting. He has no particular pain in these spells, but considerable soreness and heart-burn. He has had malaria in the past.

Examination shows a well-developed and well-nourished man, with poorly kept teeth and marginal gingivitis. All of his reflexes are highly exaggerated. No pathologic reflexes are present. Blood-pressure is 150/92. No abnormality can be detected in the chest. His abdomen is normal except for a point of extreme tenderness above and to the right of the navel. In general, no particular physical abnormality is present.

Gastro-intestinal *x*-ray examination shows no evidence of disease unless there be some slight adhesions in the appendix region. His Wassermann is negative. The blood shows 10,400 white cells, with a normal differential count, and a mild secondary anemia. The urine is normal. Stomach contents show a constantly low acidity averaging 21 total, and 12 free acid. The stools show a heavy infestation with giardia, and a few cysts of Entamœba histolytica.

For purely experimental purposes this patient was given two courses of carvacrol. Each course was preceded by three days of liquid diet and salts; 60 minims of carvacrol were given, in capsules once and in emulsion once. No effect could be seen on the parasites present. Carvacrol is a heavy, oily, doubly distilled liquid with a hot, burning taste. It is an isomer of thymol. It has been highly recommended in the treatment of hookworm, as being less toxic and more efficient than thymol. Our experience with its use in hookworm is distinctly not encouraging. We use thymol in the treatment of flagellate infections, and it is our opinion that in these conditions thymol is much more effective than carvacrol. Our experience with this treatment, however, is very limited, and further report will be made when more cases have been treated.

After a thorough course of treatment in the patient under discussion the amebas have been eliminated and a clinical cure has followed. A few giardia cysts are still seen at intervals. Further treatment will be directed toward final removal of the giardia.

Case VIII.—G. W. W. This young man is a thin, poorly nourished teacher, aged twenty-six, who has never enjoyed

robust health and has been treated for years for various nervous complaints. After leaving the army three and a half years ago he had an illness attended by fever, diarrhea, and loss of weight. Since than he has had frequent spells of diarrhea, often with mucus in the stools, but never blood and never pain. He has suffered from excessive flatulence and has gradually become more and more nervous. He has palpitation and is emotional. Physicians who had seen him had found the blood and spinal fluid normal, and nothing radically wrong with the nervous system or other organs. A stool examination had never been made.

On examining the stools there was revealed a heavy infestation with Entamœba histolytica and giardia. He was given an intensive and severe course of treatment which entirely eradicated both parasites. He has already improved greatly in every way and has taken up a more arduous and technical line of teaching from which his poor health had hitherto held him back.

We come finally to the best advertised and best studied of the intestinal protozoa, the ameba.

AMEBIASIS

By amebiasis we mean, in the original words of Musgrave and Clegg, "a state of infection with amebas." At least five varieties of amebas are known to infect man. To show the biologic relations of the various parasitic protozoa and to classify the parasitic amebas the table on page 406, modified from Dobell, is useful.

Of the general class of amebæ, only one ameba has been generally recognized as pathogenic. This is Entamœba histolytica. Kofoid and Swezy have recently described as Councilmania lafleurii a variety of ameba which they believe to be pathogenic and hitherto confused and identified with E. coli. We have studied this type of organism at length and have noted it clinically. We are not yet prepared to express an opinion on its biologic separation from E. coli. While only the E. histolytica is definitely incriminated for its pathogenicity, we believe, as already stated for the protozoa in general, that any ameba is

Sub-kingdom.	Phylum.	Class.	Genus.	Species.
Protozoa.	Rhizopoda.	Amebæ.	Entamœba	coli histolytica councilmania (?)
			Endolimas	nana
			Iodamœba Dientamœba	biitschlii fragilis
	Mastigophora.	Flagellata.	Trichomonas Chilomastrix	hominis mesnili
			Giardia	intestinalis
	Sporozoa.	Coccidia.	Eimeria	
			Isospora	
	Ciliophora.	Ciliata.	Balantidium	coli minuteum

dangerous potentially if not actively. Therefore it seems to us the wisest and safest course for the patient to have any amebic infection eradicated.

Amebiasis is wide-spread in California and in the United States. It has been estimated that 10 per cent. of the human race are infected, and it is known that practically no race of man is exempt. Clinical reports of amebic infection have increased rapidly in the last few years. The experience and reports in California of Barrow, Gunn, Kofoid, and others demonstrate the prevalence of amebiasis in this state and its serious clinical concomitants.

Until recently amebiasis was considered a strictly tropical malady, and dysentery was almost its synonym. Now we know that it is cosmopolitan and that dysentery may be of secondary importance or absent. One of us (Reed, Alfred C., Cal. State

Med. Jour., August, 1922) has called particular attention to a feature of amebic infection which is especially prominent in California. This is denoted as non-dysenteric amebiasis. By dysentery we mean merely a symptom group of more frequent evacuations containing blood and mucus and attended by pain. Such a syndrome is non-specific and non-pathognomonic (Reed, Alfred C., to appear in Amer. Jour. Med. Sci.). While clinical dysentery and amebic abscesses are considerably more frequent as a result of intestinal amebiasis in the tropics, we find in cooler climates that the non-dysenteric types prevail.

In non-dysenteric amebiasis, referring specifically to histolytica, the infection presents an approximate balance between parasite and host, and is apt to manifest itself by symptoms which are not associated with dysentery or even looseness of the bowels. So far as we know Entamœba histolytica finds its sole portal of entry into the body by way of the intestine. We know that from this ulcerative focus it can invade the blood- and lymph-streams. Having in mind the four available mechanisms for producing symptoms which were described for intestinal protozoa in general, it is not surprising that we should find non-dysenteric amebiasis where parasite and host live in a balanced relation which is the best possible for both, exhibiting such unexpected symptoms as severe constipation, neurasthenia, anemia, physical depression, malnutrition, loss of weight, indigestion, vague aches and pains, and all manner of indefinite ill health. These are associated with non-dysenteric amebiasis and disappear with eradication of the ameba. Consideration of the clinical symptoms alone may lead the observer far astray. So often has this experience been observed that we feel it desirable to enunciate once more three clinical rules which have been constructed on a basis of experience:

1. Remember that amebiasis, like protozoal infection in general, is prevalent in California.

2. Investigate every gastro-intestinal case for the presence of amebas or other protozoa.

3. Every patient with an obscure or incompletely diagnosed trouble must be suspected of harboring amebas or other protozoa.

ENTAMŒBA HISTOLYTICA
(Entamœba Dysenteriæ)

In fresh liquid stools and on a warm slide Entamœba histolytica is a characteristic active organism. It is seen to progress

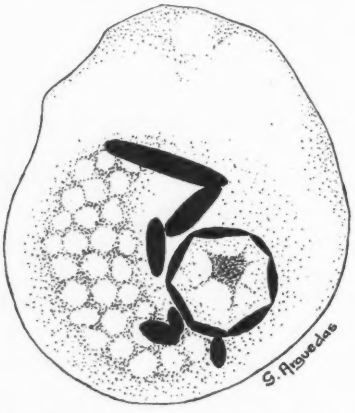

Fig. 96.—Entamœba histolytica. Rounded-up form.

across the field as if with a definite objective. The pseudopodia which it throws out almost continuously in the direction of

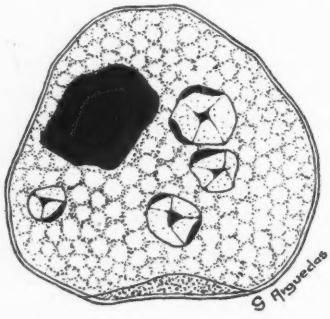

Fig. 97.—Entamœba histolytica, encysted form.

progress show little differentiation from the grayish, finely granular protoplasm.

At other times it is less active, progressing but little in any direction. It becomes more or less rounded and throws off hyaline pseudopodia, only slowly to draw them back and to form others at some other point.

The nucleus is generally very indistinct or hardly discernable. Inclusions are frequently present, most often in the form of tissue fragments or red cells which appear to be engulfed unchanged. Under less favorable conditions complete rounding occurs, and pseudopodia cease to form, in which condition the organism may so closely resemble an epithelial cell as to be indistinguishable except by the finer staining methods. Cysts in this species are small spheric bodies with a definite cyst wall and, when typically mature, contain four nuclei. There are also often present thick rods or more irregular masses of chromatin-bearing material and sometimes globules of glycogen. Infection is the result of swallowing cysts.

ENTAMŒBA COLI
(Amœba Coli)

Usually about the size of Entamœba histolytica, this species is generally less active and makes less actual progress. The rather poorly defined pseudopodia which are pushed out from a more or less rounded and unextended organism, as if at random, are but slightly different in texture from the remaining cytoplasm. The cytoplasm is granular and often contains numerous inclusions derived from material available in the feces. Red cells, however, are not seen. The nucleus is generally more clearly discernible than in Entamœba histolytica.

Mature cysts of this species typically contain eight nuclei and are ordinarily somewhat larger than those of Entamœba histolytica. Sometimes chromidial bodies, more commonly in the form of splinter-like bars, are present.

In two years' experience by one of us in the Yale Hospital in Yunan Province in central China dysenteric amebiasis was found to be most common. The following case is typical of hundreds and illustrates the usual course of intestinal infection with Entamœba histolytica in a hot climate.

Case IX.—A well-nourished Chinese boy of ten years was admitted to the ward with a history of diarrhea for four months, accompanied by much mucus and blood. The movements averaged from six to eight daily and were attended by some colicky pain and severe tenesmus. Examination of the stools showed enormous numbers of motile Entamœba histolytica, and a few ascaris ova. The ascarids were expelled with calomel and santonin. Then ½ grain emetin was given daily hypodermically. In four days there was a complete relief of symptoms and the patient was discharged.

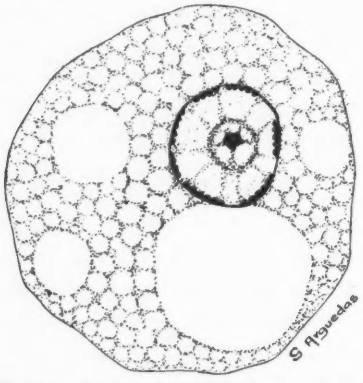

Fig. 98.—Entamœba histolytica, motile form.

Case X.—An English mercantile agent had come up on a river boat, and a week before had laid over two days for hunting. For three days he had severe diarrhea, ten to twelve evacuations daily, with grayish, bloody mucus, and considerable abdominal pain. His temperature was normal. Microscopic examination of the mucus showed swarms of actively motile Entamœba histolytica. He was given ½ grain emetin hypodermically twice daily. On the fourth day all symptoms disappeared, he felt perfectly well, and was dismissed.

The really wonderful clinical improvement in these two cases was fairly typical of the results of emetin administration in acute amebic dysentery. Yet neither case was cured. And

it is doubtful if hypodermic emetin alone ever did cure an amebiasis. Its effect on the acute florid symptoms is somewhat analogous to the effect of salvarsan on florid acute syphilis. But the infection is not eradicated and further treatment is found necessary, although urgent symptoms of dysentery disappear usually by the fourth day of treatment.

One must not forget that overenthusiastic use of emetin has its dangers. This has been discussed in detail by one of us (Alfred C. Reed, Boston Med. and Surg. Jour., September 14, 1916). Not infrequently the overoptimistic therapeutist will see enteritis, diarrhea, muscular weakness, breathlessness, and evidences of a poisoned myocardium when emetin has been administered unduly long.

Case XI.—Mrs. G. D. This patient is a housewife, aged thirty-two. She has had chronic indigestion since girlhood. Her symptoms have been nausea, epigastric pain, sour eructation, heart-burn, a tendency to syncope, and extreme consciousness of gastric discomfort. She has had her appendix removed and a forward placement of the uterus. Her indigestion has been much worse in the last five years, and its seriousness is progressive. Her bowels always move freely and regularly. She has never had diarrhea or dysentery. At the time of her laparotomy by Dr. M. E. Rumwell, three months ago, the gall-bladder was grossly normal and there was no gross lesion discoverable in the stomach or intestines other than a thickened, inflamed appendix. A number of rather large lymph-nodes were seen in the peritoneum and lesser omentum. In the last two or three years her weight has steadily increased to 174 pounds. She is 5 feet, 4 inches tall. She has thyro-ovarian insufficiency.

Her blood shows a moderate secondary anemia. Kidney function is normal. The only abnormal laboratory finding is the presence of numerous eight-nucleated cysts of Entamœba coli. These have been identified as that variety described by Kofoid and Swezy as Councilmania lafleurii.

She is now under treatment for the amebiasis. At the same time she is taking ovarian residue and thyroxin.

We have seen a considerable number of cases of amebiasis of Kofoid's Councilmania type. The final determination as to

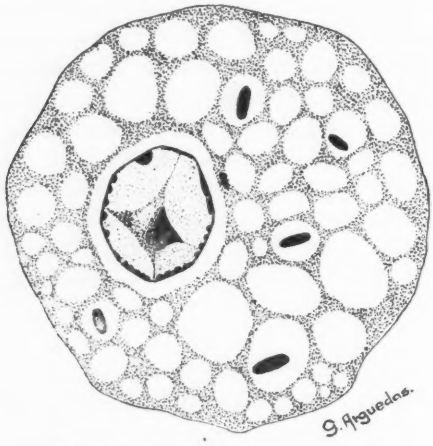

Fig. 99.—Entamœba coli, motile form.

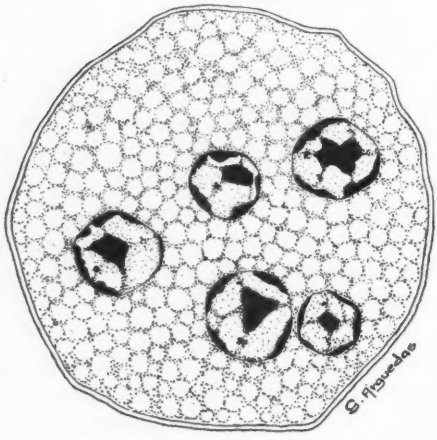

Fig. 100.—Entamœba coli, encysted form.

whether this is a new species, hitherto confused with Entamœba coli, will have to be made by the systematic protozoölogist. At

present we classify them as E. coli of the Councilmania type. The variety is easily recognized and differentiated, but further study and confirmation is needed to establish its biologic separation from E. coli. We have had no difficulty in curing this species of infection with the same treatment used for E. histolytica. In the patient under discussion the symptoms have been in abeyance since shortly after the emetin was started.

ENTAMŒBA NANA
(Endolimax Nana)

Although much smaller than Entamœba coli, the active form of E. nana somewhat resembles it.

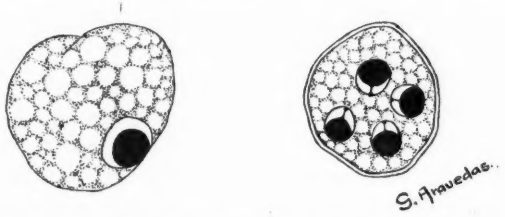

Fig. 101.—Endolimax nana. Encysted and motile forms.

As ordinarily seen in the stool, its movements may perhaps be best described as mere changes in outline occurring slowly. The nucleus is indistinct and the cytoplasm shows no marked characteristics. Motility is rapidly lost after leaving the body, the organism becoming rounded, in which condition it is practically indistinguishable in the stool without resorting to staining methods.

Small cysts are formed, typically showing four nuclei when mature.

COUNCILMANIA LAFLEURII

Under this heading Kofoid and Swezy have described an ameba which they believe to constitute a distinct and hitherto unrecognized species.

These authors believe that Councilmania has, in the past, been confused with Entamœba coli, chiefly because of the exist-

ence of eight-nucleated cysts in both forms, but that it is distinguishable from E. coli by a number of characteristics.

In contradistinction to Entamœba coli, the free stage of Councilmania is very active, the pseudopodia are formed with "explosive suddenness"; the ectoplasm is sharply separated from the endoplasm, and red blood-corpuscles are freely ingested. The structure of its nucleus as described by them differs from that of other amebas in a number of particulars.

A most important feature, in their description of the cysts of Councilmania, is a remarkable process of bud formation in which the nuclei of the cyst successively migrate into buds, which are subsequently detached.

Case XII.—Mrs. F. A. S. This patient is a housewife, aged thirty-three. She is very nervous, has hysteric outbursts, syncope, and spells of aggravated weakness. She has suffered severely for several years from backache. She has been told repeatedly that all her trouble originated in her "nerves." She is constantly exhausted, worn out, and has heavy night-sweats. She wakes every morning with sharp pain in the entire spine and neck. She faints easily and has much palpitation. Has had muscular rheumatism many times and "intestinal flu" twice in the last four years. Tonsils and diseased teeth have been removed. Digestion is usually fair, but she has spells of upset stomach, and occasionally mild diarrhea. In the past year she has had severe attacks of abdominal pain. She had an operation for hemorrhoids and fissure some two years ago. Spells of constipation more recently have resulted in a recurrence of hemorrhoids. Had jaundice ten years ago. She had no pulmonary complaints or history.

She was born in San Francisco and has always lived here. Her normal average weight up to two years ago was 145 pounds. It is now 125 pounds. Ten pounds of this has been lost in the past six months.

Examination shows a tall, spare young woman, very poorly nourished, with a weak, pliant spine. No evidence of arthritis. No adenitis. Reflexes are all exaggerated, and the only abnormal

reflex is a loss of pharyngeal irritability. No abnormalities appear except general muscular weakness, slouching posture, visceral ptosis of moderate degree, and small external hemorrhoids. Functional tests of heart, circulation, and kidneys show no abnormality. There are no signs of hyperthyroidism, tuberculosis, or organic nervous disease. Blood-pressure is 70/110.

Laboratory findings: Gastro-intestinal *x*-ray examination shows only a very moderate dropping of the colon and stomach. Urine is normal. Wassermann negative. Blood shows a moderate secondary anemia. Eosinophils are 2 per cent. Stool analysis shows abundant cysts of Endolimax nana and Entamœba coli.

This patient has shown a decided clinical improvement under antiprotozoal treatment. It is too early to report end-results.

Here, then, is a young woman condemned to chronic invalidism by physician and osteopath alike, presenting hysterical symptoms and crises, with a large amount of ill health and misery, and no satisfactory physical explanation to be found. Two observations can be made from her example. First, every obscure diagnostic case, as well as every patient presenting gastro-intestinal symptoms, should be adequately searched for intestinal protozoa. Second, if intestinal protozoa are present, that patient will almost invariably harbor some pathologic conditions which can be related to the protozoa.

This patient gives an average eosinophil count of 2 per cent. This is entirely within normal limits. It is our experience that the average blood-count in cases of infection with intestinal protozoa shows a mild or moderate secondary type of anemia and a fairly normal differential count. Leukocytosis is not present.

Case XIII.—Miss. M. S. This patient is a housekeeper, aged forty, who has always lived in the Middle West and California. Her mother died from cancer of the stomach. She has had malaria and typhoid. Eight years ago she suffered a nervous breakdown which incapacitated her for one year. For many years she has experienced abdominal discomfort after the noonday meal, usually followed by a loose bowel movement. She

has also had a constant tendency to diarrhea, and never knew what it was to be constipated. Even with diarrhea she has never noticed mucus or blood. Eighteen months ago she had an attack of acute gastro-enteritis of unknown cause. Since that date she has had several similar attacks with intense vomiting and diarrhea, but no blood or mucus. It was another such attack that brought her to our attention at this time. Her average weight is 109 pounds and she is 5 feet 5 inches tall. Severe backache, especially in the lumbar region, and paresthesias of the arms and legs complete her history.

Examination shows a poorly nourished woman with coarse, oily skin. Her teeth show apical (by *x*-ray) and gingival infection. Reflexes are highly exaggerated. Sensations are normal. Blood-pressure is 106/80. Heart and lungs are normal. Abdomen is retracted, thin, relaxed, with no local tenderness. The sigmoid is spastic and easily palpable. Stomach contour is at level of umbilicus. Right kidney is freely movable. There is no pelvic trouble.

Laboratory findings: The *x*-ray examination shows marked spasticity of the colon and stasis in the appendix. Some antral spasm is probably reflex from the colon. Gall-bladder plates are negative. The blood shows a mild secondary anemia. Wassermann negative. Urine normal. Stool analysis reveals the presence of Endolimax nana and Entamœba coli.

This patient gives a rather peculiar history. Her colitis seems to be at the root of her major symptomatology. There is no evidence of gall-bladder disease, although this comes into consideration very strongly. While the appendix might be at serious fault, it seems likely that the mild chronic appendicitis is closely associated with the spastic colitis. In such cases frequently the symptoms outlast removal of the appendix and only yield with relief of the colon irritation. In this case it is absolutely essential to dispose of the amebas before considering operation. The patient is now under treatment to this end.

Case XIV.—Mrs. V. P. Referred by Dr. Brett Davis, of Merced, and Dr. H. A. Stephenson. This young woman, aged twenty-five, is six weeks pregnant, and states that her general

health was excellent until the birth of her first baby four years ago. Since that time she has felt weak and run-down, has lost 15 pounds in weight. Following the first confinement she was quite constipated up until the past six months, when she has had spells of diarrhea attended with considerable colic, and with much mucus in the stools. She has never noticed blood. She gets faint at times and has occasional spells of nausea. The present pregnancy, which is her second, has made so far no change in her symptoms.

Examination shows no abnormality in the heart or lungs. Blood-pressure is 122/80. Pulse averages 80. She has very large postcervical glands and her thyroid is a little enlarged. Reflexes are exaggerated. The abdomen is soft and relaxed with a palpable right kidney and tenderness over the transverse and descending colon.

Laboratory findings were normal except as noted. There was a secondary anemia, 3,900,000 red cells, with 80 per cent. hemoglobin. Stool examinations failed to show protozoa, but, as we felt certain of their presence, the examinations were continued. The specimen of the ninth day showed eight-nucleated cysts of Entamœba coli of Kofoid's Councilmania type.

We have yet to find a person harboring intestinal protozoa who has not some symptomatic or objective disturbance which can be related in some way to the protozoa. Unfortunately, we cannot always find the protozoa in every patient who presents a suggestive clinical picture. In this case persistent search revealed them. This serves to illustrate the need for adequate examination for protozoa in all gastro-intestinal and obscure cases. Constipation is more commonly seen than dysentery in the amebic cases in California. One patient last year had lived in seven large cities of the South and Southwest, and over a period of several years was treated in each of those cities for obstinate constipation. Discovery of Entamœba histolytica and its eradication cured the constipation.

Case XV.—H. B., a Porto Rican, male, aged twenty-three. This is one of the most interesting patients we have had. His

complaint was malaria. He left Porto Rico at the age of twelve, was in New York two years, Georgia, eighteen months, then in succession worked in Virginia, Alabama, Arizona, and Texas. Two years ago he came to San Francisco and has been here since, except for short trips into the Sacramento Valley.

He has had smallpox in Porto Rico and flu in the epidemic of 1918. He has had several attacks of severe sore throat. He had Neisser infection five times and denies lues.

According to his history the present illness began three months ago with a sharp attack of malaria contracted in the Sacramento Valley. Severe chill and fever appeared on alternate days for a month. The malaria was not controlled until after his return to San Francisco.

Physical examination shows a dark-skinned young man of slight build. The tonsils show a chronic inflammation. His teeth are in bad order. The axillary, cervical, epitrochlear, and inguinal glands show a uniform moderate enlargement. No abnormality in chest. The spleen is considerably enlarged and palpable. The liver edge is felt one fingerbreadth below the ribs. The abdomen is distended and tympanitic, no fluid demonstrable. He has a prostatitis, also non-purulent otitis media. Except for the points noted the examination was negative.

Laboratory findings: Blood, an average count showed 2,100,000 red cells with 50 per cent. (Sahli) hemoglobin. The red cells show polychromatophilia, anisocytosis, and poikilocytosis. One normoblast was seen and there were very numerous subtertian signets. White cells, 4000. Polynuclears, 62 per cent.; lymphocytes, 23 per cent.; large mononuclears, 7 per cent.; transitionals, 4 per cent., and eosinophils, 4 per cent. Blood Wassermann is positive. Stool analysis shows larvæ of Strongyloides stercoralis, ova of Tænia nana, and Schistosoma mansonii and cysts of Entamœba histolytica. The diagnosis, therefore, is as follows:

1. Gonorrhea and prostatitis.
2. Chronic tonsillitis and otitis media.
3. Syphilis.

4. Subtertian malaria.
5. Tænia nana.
6. Strongyloides stercoralis.
7. Schistosoma mansonii.
8. Entamœba histolytica.

We feel certain that the diagnosis is complete and no parasites have been overlooked.

Treatment consisted first of a course of quinin which was sufficient to control the symptoms, eradicate the plasmodia from the circulating blood, and prevent relapse for the seven months under observation. He was then given a course of intravenous tartar emetic, receiving a total of 35 grains, doses being at three-day intervals and the maximum dose 2½ grains. Then came a routine cestode treatment, consisting of 90 grains of felix mas in two doses an hour apart, with the usual preparation of liquid diet and salts for two days. After this treatment the trematodes were not seen for two months. Schistosome ova then reappeared and all the other parasites were apparently present in their original numbers. The next course of treatment will be aimed at the ameba.

Several comments come to mind in connection with this patient. It is to be noted that 35 grains of antimony salt were useless in removing the schistosome infection. Such a course is generally considered curative, especially in the urinary type. But it is doubtful if the intestinal or mansonian schistosome found here should be any more resistant. The multiple infections in this man illustrate very beautifully a rule of clinical practice which is even more valuable in the diseases of hot climates than in temperate areas. Do not stop with the first abnormal condition discovered. Complete the thorough full examination and make it a routine. In this patient the finding of malaria was sufficient to explain his symptoms and physical findings. Only with the result of the Wassermann test did syphilis come into view. The first stool examination showed schistosome ova and strongylus larvæ. But two intestinal infections being demonstrated, it was considered that there might well be more, and further examinations justified this

consideration. It is remarkable that the numerous parasites present and which had probably been present for a long time should be associated with only 4 per cent. eosinophils, a figure not above the normal. In spite of the presence of Entamœba

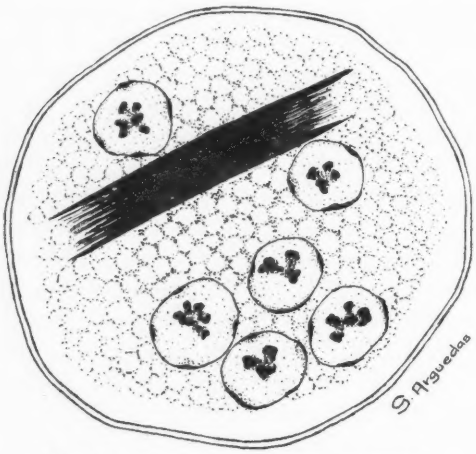

Fig. 102.—Councilmania lafleurii, encysted.

histolytica and Schistosoma mansonii the patient gives no history either of diarrhea or of dysentery.

EXTRA-INTESTINAL AMEBIASIS

In the consideration of amebic infections of man it is worthy of our attention that amebas have been described in many extra-intestinal locations. Most of these descriptions do not carry the stamp of authority when analyzed. We recognize, of course, the part played by Entamœba histolytica in the production of abscesses in the liver, brain, and lungs. An interesting comment on the ameba of abscesses is the absence of encysted forms in such lesions. Even in intestinal ulcers cyst formation is variable, but in abscesses cysts are not found. The cause of this phenomenon is veiled in obscurity, but doubtless is related to the lack of drainage of the necrotic material.

This results in the absence of any means of transferring the infection to a new host. Such transfer is absolutely essential if the amebic race is to persist. Transference of amebas is a function of the encysted form alone. Under no natural circumstances, we believe, is amebiasis transferred through the agency of motile amebas. Therefore the sole purpose of cyst formation must be the propagation and continuance of the amebic race from man to man. Lacking any opportunity for such propagation, as is the case in amebic abscesses, we judge that the biologic stimulus to encystment is lacking and cysts are not formed.

Aside from these recognized extra-intestinal occurrences there have been many reports of the presence of Entamœba histolytica in the urine and in the urinary bladder. A few of these reports are undoubtedly accurate, but, as has been detailed elsewhere (Reed, Alfred C., Cal. State Jour. of Med., August, 1922), perusal of most of them leads to the conviction that inflammatory or body tissue cells have been confused with amebas. We must recall that normal white blood-cells have an active ameboid motility and a cytology to be distinguished with the utmost difficulty in fresh preparations from motile amebas. Herbert Gunn has demonstrated to us the close similarity of fresh white cells to wandering tissue cells, pus-cells, and amebas. To exclude error in differentiation, study of the free-moving forms must be supplemented by study of cysts when they can be obtained, recognition of the nuclear structure, and observation of stained preparations. Most writers who have described amebas in the urinary tract have not employed these precautions. These remarks might be directed with equal force to the description of amebic lesions of the skin and other non-abscessed regions. We cannot yet give a final opinion as to the occurrence of amebas in the bile-tract. Gunn has reported a case in which intestinal amebiasis cleared temporarily after removal of a gall-bladder which apparently contained motile amebas. Recurrence of intestinal infections might have been derived from infection in the biliary ducts. It has been supposed that amebas cannot live in the

presence of bile. In this case we have to consider, then, the possibility of confusion between leukocytes in the bile and amebas. We have also to remember that the suggestion in this case of biliary amebic infection presupposed free discharge and drainage into the intestine and thereby established a means of amebic propagation to new hosts. Under such conditions it would be expected that cysts would appear at times, yet none were found. It seems uncertain, therefore, whether we can consider the biliary tract under any circumstances as an amebic habitat.

The appendix must also be considered as a frequent hiding-place for amebas. Many so-called incurable cases of intestinal amebiasis undoubtedly depend on an inaccessible amebic focus in the appendix. It is to be expected, if this be true, that in these cases removal of the appendix, combined with routine anti-amebic treatment, would be just as effective and much less burdensome than appendicostomy with a long period of colonic irrigations through the appendix.

RELATION TO ARTHRITIS

We come now to the suggestion which has been put forward at the Stanford Medical School, that amebas have a definite relationship to arthritis deformans, which is Ely's second great type of arthritis.

This subject has received a great deal of attention from Leonard Ely and ourselves, especially during the past year. Many writers in the past have claimed a relationship between arthritis and amebiasis, but no one ever got beyond the stage of speculation. More recently Barrow has claimed that every case of hypertrophic arthritis is accompanied by the presence of protozoa in the intestinal tract.

Undoubtedly the most accurate and serviceable classification of chronic arthritis is that put forward by Ely. He divides all chronic arthritis into two great types. These types differ sharply in etiology, pathology, clinical behavior, and *x*-ray appearance. Type I includes all of the frank bacterial infections, tuberculosis, syphilis, typhoid, pneumococcus, coccid-

ioides, streptococcus, etc. It also includes so-called atrophic arthritis. The basic lesion in this type is a proliferative inflammation in the synovial membrane, in the bone-marrow, or in both. It tends toward complete cure or at least results in fibrous or bony ankylosis. *x*-Ray plates show rarefied bone, thinning of the cartilage, and absence of new bone production.

In his second great type Ely places a definite group of arthritides sharply distinguished from the preceding. This includes what has been formerly named arthritis deformans, hypertrophic arthritis, osteo-arthritis, and senile, degenerative, or metabolic arthritis. "It is the chronic rheumatism of the elderly. Its cause is unknown. Its primary pathologic lesion is an aseptic necrosis in the bone and marrow in the immediate vicinity of the joint. As a result of this necrosis in the marrow new bone is laid down at the joint surface, and especially at the lines of attachment of the capsule. This gives rise to the well-known spurring and lipping, so prominent in the *x*-ray picture and in the pathologic specimen, and is responsible for most of the names bestowed on the disease. The joint becomes mechanically damaged by the deformed and distorted bone ends, but the disease practically never results in either bony or fibrous ankylosis except in spinal involvement. The new bone formation is permanent. Hence a joint once the seat of this disease never returns to normal, even if symptoms disappear."

Ely has noted an almost constant relationship between the presence of Type II arthritis and the previous existence of alveolar infection in the jaws. He claims symptomatic improvement in many cases after removal of teeth.

Ely's description of Type II, as just quoted, serves to lay great emphasis on the need for discovery of the specific cause of this disorder, so that treatment may be preventive and may be instituted in time to save the joint from permanent bony damage. It is possible to say clearly that this second type of arthritis is not bacterial in origin. In reviewing possible causes, then, outside of bacterial, we are confronted with very few possibilities. The pathology, as shown by Ely, does not con-

form to that of bacterial invasion. Metabolic causes have been suggested, but the whole nature of the disease removes this from serious discussion. This theory has finally been disproved by calorimetric studies in DuBois' laboratory, where it was found that the metabolic rate is normal. Whatever causes this arthritis, it is accompanied by normal basal metabolism

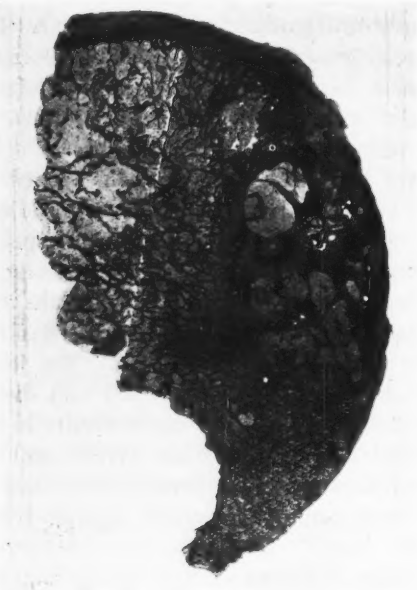

Fig. 103.—Photograph of section of necrotic bone from Ely's case of Type II arthritis. Note area marked, where photomicrograph in Fig. 104 was made.

and by absence of toxic destruction of protein (Cecil, Barr, and Dubois, Arch. Int. Med., May, 1922). An invading organism is strongly suggested by the nature and location of the necrosis. Excluding bacteria, we have been led to feel that protozoa offer a possibility worthy of careful study.

Following out this idea, Ely removed the head of a femur in this type of arthritis. "Sections from the necrotic areas

of this bone were stained with a standard hematoxylin method and showed numerous cellular bodies identified as Entamœba histolytica (Ely, Reed, and Wyckoff, Cal. State Jour. of Med., February, 1922). These bodies were abundant near the periphery of the necrosis and especially abundant around the capillaries."

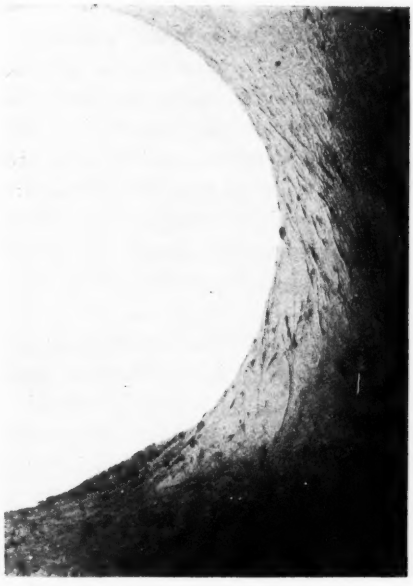

Fig. 104.—Photomicrograph of portion of wall of dead or cystic area of Ely's specimen 225. (See Fig. 103.)

Their identification as amebas has not met with unanimous confirmation from those who have examined the sections. They were studied by Kofoid and Swezy (Cal. State Jour. of Med., February, 1922), who make the following statement: "A portion of the head of a human femur removed by operation in a case of arthritis deformans . . . reveals a pure infection of amebæ about the characteristic lesions in the bone. No stained bacteria have been found in our examination. . . .

The organisms interpreted by us as amebæ are unlike known normal or pathologic tissue cells. They have the clear nuclear structure of Endamœba dysenteriæ (Councilman and Lafleur) found in tissues about amebic ulcers in intestinal amebiasis. Their nuclei are unlike those of Endamœba gingivalis."

In a later report (Univ. of Cal. Publications in Zoölogy, April 21, 1922) Kofoid and Swezy present a critical study of these organisms, reaffirming their first opinion. As has been stated, a possible relation between ameba and chronic arthritis has been suggested many times in the literature of the last decade. Barrow has emphatically stated his belief that chronic arthritis would be found related to intestinal protozoal infections. A theoretic review of possible causes made it appear logical that protozoa might supply the missing key to the etiology. The following case, illustrative of several whose records we now have, gives the clinical side of the matter.

Case XVI.—W. C. D. In the late summer of 1921 Barrow found Entamœba histolytica in the stools of one of Ely's patients who suffered from a hypertrophic arthritis of the spine. Relief or improvement did not follow the ordinary methods of treatment. A spinal harness, immobilizing apparatus, massage, baking, etc., brought no benefit. He was then put on a course of specific anti-amebic treatment, with a remarkable and immediate clinical improvement. One relapse of arthritic symptoms was coincident with recurrence of cysts in the stools, and the pain and stiffness at once disappeared with resumption of treatment. A second relapse was not accompanied by any evidence of intestinal amebiasis, but improvement again followed resumption of amebic treatment. Such a course would be entirely logical if we can assume the presence of protozoa, in this case Entamœba histolytica, as the causative organism in the spine. Complete eradication of protozoa from the intestine would not at all mean their concurrent eradication from the bony lesions. This patient has now for more than six months had no arthritic symptoms and has very good motility and use of his spine. He considers himself cured.

Case XVII.—G. F. This man is a Norwegian miner and laborer, forty-three years old, who came to the United States fifteen years ago. He worked as a deep ore miner until the last four years, in which he has been employed as a railroad laborer. He has had malaria, typhoid, chancroid, and gonorrhea. He also has just had some dental infections cleared up. His immediate condition consists of a Type II arthritis of the right knee. This came on something more than a year ago. His blood-count is normal. Wassermann is negative. Stools show cysts of both Entamœba coli and Entamœba histolytica. No gastro-intestinal history was elicited.

Under a course of treatment for amebiasis the inflammation in the right knee was very considerably aggravated. After the treatment was terminated the pain, stiffness, and incapacity in the joint was so extreme that baking, strapping, and vaccines were resorted to for relief. We could not escape the impression that there was a close relationship between the progress of the treatment and the exacerbation in the knee. While the amebas were eradicated from the stools, the treatment apparently excited and stirred up the inflammatory focus in the knee. This might be understandable if the osteo-arthritis were amebic in origin. Otherwise it is difficult to explain.

Case XVIII.—Mrs. S. R. B. We must refer at this point to another patient with well-marked hypertrophic arthritis of spine, hips, and knees. Exhaustive search showed no intestinal protozoa. She had suffered from the arthritis for thirty-five years. A course of anti-ameba treatment gave her great clinical improvement and relief of pain. It was considered that this result was explained best by the free elimination secured by the treatment. This is in accord with the improvement often observed following the use of colon irrigations and a diet designed to decrease intestinal putrefaction. We believe that amebic infections of the bowel are permanent unless eradicated by specific treatment. It is possible that the same is equally true of all the intestinal protozoa. Nevertheless, we must take into account the possibility that the protozoa may disappear from

the intestinal tract while gaining a foothold elsewhere in the body. Such a circumstance would meet the criticism that all cases of hypertrophic arthritis do not give evidence of intestinal protozoa.

At present we cannot prove that the specific cause of Type II arthritis is protozoal. We have, however, sufficient data to justify careful study of the subject. It is especially to be desired that this thesis should be critically considered in other laboratories and clinics. Hypertrophic arthritis is one of the most common, most disabling, and most painful conditions to which man is subject. We have here a field worthy of serious study after all other suggestions of cause thus far have proved fallacious.

While protozoa have been associated with various unusual clinical conditions, time forbids further detailed discussion of them. We wish to present briefly, however, one striking case of the association of

AMEBA AND ASTHMA

Case XIX.—Miss F. S. This patient was seen and followed through the kindness of Dr. W. H. Barnes, whose detailed case report will appear at a future date. This young woman, a trained nurse, was in good health until her duty as an army nurse during the war. With no previous history of significance she suddenly developed unusually severe paroxysms of asthma. These attacks recurred at frequent intervals for five years. During the same period she had recurring spells of diarrhea and sometimes of dysentery. No cause for the asthma could be found after exhaustive study. No foci of infection were discovered. Climate and season did not decrease its severity. Eventually examination of the stools revealed a massive infection with Entamœba histolytica. Specific treatment for the amebiasis resulted in immediate but temporary disappearance of the ameba and absolute freedom from asthma. Owing to unavoidable circumstances she did not receive an intensive or curative amebic treatment. For two years there was reappearance of slight diarrhea and cysts, at once accompanied by return of the asthma. Emetin gave prompt relief from the asthma each

time. Finally a more severe course of treatment for the ameba became possible, and she promptly developed a multiple acute arthritis of the large joints. This gradually subsided. Cysts disappeared from the stools. Without warning, some months later, asthma recurred with great severity. No cysts could be found in the stools. Treatment with emetin this time had no influence on the asthma, which was controlled with the utmost difficulty by the use of adrenalin, atropin, and morphin. Pelvic examination now showed a mass in the region of the right adnexa. Dr. S. F. Cowan by laparotomy removed a fibroid uterus and right cystic ovary. Recovery was rapid and asthma has been absent for a space now of three months.

TREATMENT

The subject of treatment has been omitted from the discussion thus far because its conduct is subject to great dispute and variation. It is our custom to use a fairly standard course of treatment for amebiasis, this course being modified to meet the requirements of the individual patient. The standard calls for six to ten days of emetin hydrochlorid, 1 grain hypodermically daily. A moderate dose of neosalvarsan is then given in the vein. On the following six days the patient receives daily 3 grains of bismuthous emetin iodid by mouth. This drug is difficult to give and requires frequently various special measures to insure its retention. If possible, it is given in gelatin capsules, otherwise in salol-coated pills. After this course a second neosalvarsan dose is administered. In the third week a mild ipecac preparation is given, either alcresta ipecac, a half-dozen pills daily, or small amounts of ipecac powder in salol-coated pills. The final neosalvarsan terminates this week. Further extension of treatment is based on the recurrence of cysts in the stools.

In chronic cases of long standing, especially with history of ineffective treatment, the course is introduced by a week in which massive doses of ipecac powder, up to 100 grains, are given once daily for not over five days. If ulceration is much in evidence colon irrigations are used, quinin or thymol, 1 : 2000

solution, using 1 gallon of fluid. Sometimes under these conditions oil enemas containing thymol or aristol and camphor prove effective. We have no faith in the action of so-called intestinal antiseptics, and it is doubtful if they can particularly influence the bacterial flora of the intestine. They are worse than useless as far as concerns their effect on protozoa. Frequently great benefit in treatment attends the regulation of diet to relieve fermentation or putrefaction in excess. Also digestive ferments or stimulation of bile flow may be needed.

For the flagellates and ciliates we add to the above two courses of thymol in divided doses. The treatment of these organisms (flagellates and ciliates) is most unsatisfactory and difficult. Not infrequently they resist all treatment.

CONCLUSION

With increasing clinical experience we are convinced that intestinal protozoa have been neglected to the detriment of many patients. We believe the patient's expectation of health is invariably lowered by the presence of protozoa and, therefore, that none of them can be considered harmless or safe. The degree of their pathogenicity is in part determined by their species, and to an unknown degree by other circumstances, such as mass, resistance of host, and other biologic factors at present but poorly understood. Protozoal infections are surprisingly frequent. No gastro-intestinal case or patient with an obscure diagnosis should be held as adequately studied until proper search has been made for protozoa.

CLINIC OF DR. LANGLEY PORTER

DEPARTMENT OF PEDIATRICS, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

DERMATOPOLYNEURITIS (THURSFIELD, PATTERSON), ACRODYNIA (WESTON), ERYTHREDEMA (SWIFT)

THE patient who is presented is an undernourished male child twenty-two months of age. You will note the peculiarity of his position, which is an exaggerated knee-chest posture. The hair is scanty, dry, and on the right side there is an area from which tufts have been plucked by the patient. This hair pulling is indulged in quite often. You will also see the beads of perspiration upon the face and note that perspiration has soaked the child's pillow and his sleeping garments.

The expression of the face is quite remarkable—difficult to describe—sullen discontent perhaps is descriptive enough, although apathy also is revealed by the facies. The coryza that interferes with breathing is obvious, also the tendency to bury the face in the pillows, although that this latter is an evidence of photophobia may be doubted. On the skin of the right cheek there is this irregular dark red spot 2 inches in diameter, not raised, without definite border, darker in its center, fading toward the periphery. It is covered with yellowish-brown scales. A patch of similar appearing rash shows on the right thigh and there is a definite but quite different looking involvement of the skin of the hands and feet. This part of the skin eruption is important and of much interest. The hands and feet look to be slightly swollen. They show a mild degree of cyanosis, yet there is also a reddening of the soles and palms and of the dorsal aspects of fingers and toes. Desquamation is taking place over both palms and soles and along the fingers to their tips, pro-

ducing these innumerable tiny white areas of shedding epithelium. The resulting appearance is best described as worm eaten. Desquamation is also evident about the nails and there has been secondary infection sufficient to cause a mild degree of paronychia. The nails themselves are brown, dry, and grooved. The swelling and redness in this case extends no higher than the wrist and ankle on the one surface and the middle of the dorsal aspects on the other.

When one disturbs the child, its apathy gives way to irritability and its resistance becomes extreme. The edematous appearing swelling of the hands and feet proves not to pit on pressure, but blanching of the skin does result. Separating the fingers, numerous small blebs can be seen, and a few smaller blebs present on the palms and soles show that the desquamating circles succeed the drying up of such vesicles.

On handling, there is notable hypotonicity. There is especially flaccidity of the neck muscles. The head is held erect with difficulty. The reflexes are all present, but they are difficult to elicit. This is especially true of the knee-jerks. The eye reflex to light is unaltered.

The mouth shows this moderate degree of gingivitis. The throat seems normal, although the tonsils are larger than those found usually in the throat of a twenty-month-old baby. There is a well-marked coryza. These are the only marked peculiarities to be determined upon examination.

Examination of the heart, except for the rapidity of the pulse, doubtless due to excitement, reveals no abnormalities. The lungs also are without evidence of pathology. Abdomen and abdominal contents likewise show no discernible departures from the normal. There is, however, definite but slight enlargement of groups of lymphatic glands, cervical, inguinal, and axillary.

So much for the appearance of the patient. Let us turn to the chart. Here we learn that a von Pirquet test has been made and has failed to react positively, although an intradermal test was followed by what is noted as a faintly positive reaction.

Blood examination: The hemoglobin is recorded as being 96 per cent.; red cells, 5,500,000; white cells, 11,800. The differential count is without significance, although the polymorphonuclear cells are proportionately more than is usual at this child's age (66 per cent.).

The results of the urine examination are likewise of little value to us, for except a slight trace of albumin they reveal nothing abnormal. On one occasion when the child was having a great deal of sugar in his food it was noted that sugar appeared in the urine. As this occurred only once this finding can be disregarded.

Nose and throat cultures show only staphylococci and Micrococcus catarrhalis.

The aid of the radiographer was invoked, and chest plates showed no involvement of heart or lungs, while from a screen examination of the abdomen it is reported that tone and position of the stomach were correct and peristalsis of the intestine normally active. Electrocardiographic tracings are essentially negative. An *x*-ray plate showed the bony structures of the hands to be free from abnormality.

Tests for protein sensitization also were made, and to none of the proteins used did the child react. These included proteins of streptococcus, hemolytic and viridans, and Staphylococcus aureus, Freidländer's bacillus, Hoffman's bacillus, Micrococcus catarrhalis, as well as those of a variety of common foods.

Bacteriologic investigation of the stool showed a predominantly proteolytic flora.

Investigation of the blood chemistry showed plasma Co_2 51 vol. per cent.; urea, non-protein nitrogen, creatin, uric acid, glucose—all within normal limits.

Blood Wassermann reaction negative.

The temperature curve you see runs along between 37° and 38° C. The weight curve descends abruptly after admission and afterward continues without much change one way or another.

Let us now turn to the history of the child's illness. The birth was normal, unaccompanied by untoward events. The mother's breast supplied all the baby's food for its first five

months. During the first year its development was that of a normal child and it remained in perfect health until a febrile attack, which was diagnosed influenza, occurring three and a half months ago, lasting twelve days. There was an interval of apparent health lasting another twelve days. At the end of this time the child was seized with abdominal pains of such severity that it screamed from agony. This attack lasted two days, when it disappeared. Similar attacks have plagued the child from time to time up to now. During these attacks the child adopted unusual positions, especially the knee-chest position, and he was found frequently wringing his hands and rubbing his feet one against the other and against the bed and bedding. Shortly after this the swelling, redness, and vesiculation of the hands were noted; a little later a fine rash consisting at first of tiny erythematous points and later of small vesicles on a generally reddened skin. The drying of these vesicles in turn brought about a drying and branny superficial desquamation of the skin, especially over the abdomen. The itching became intense. The child scratched the area of eruption, and because of the distress engendered it became sleepless at night, restless, and irritable in the daytime. The rash on the body has now largely dissipated, and only the affection of the hands, feet, buttocks, and one cheek remains visible. At the time the eruption was at its height there was a marked gingivitis and a few ulcers were seen on the mucous membrane of the gums and cheeks. All the while it has suffered this child has been constipated.

We have, therefore, before us a child who presents an unusual clinical picture characterized by evidence of changes in its nervous, cutaneous, dental, and gastro-intestinal tissues, as well as temperamental and psychic changes. Paresthesias, diminished reflexes, cold extremities, vasomotor changes most apparent in hands and feet, profuse sweating, possible photophobia, alternating apathy and irritability, adoption of peculiar positions, and extreme hypotonus testify to the probable involvement of the nervous system, at least of the peripheral nerves.

The picture, while unusual, is characteristic of a disease to be met with occasionally among children. Apparently the condition is more common or more often recognized on the Pacific slope than elsewhere in this country, although case reports with increasing frequency have emanated from every section of the United States and Canada as well as from Australia and England.

In fifteen years I have seen 12 cases, but not until recent years has the condition been recognized as a clinical entity with a definite given name.

The Name of the Disease.—The names acrodynia and erythredema have been proposed for the disorder. Neither seems particularly fitting, as both emphasize less fundamental symptoms and ignore the neurologic changes which are uniformly to be found accompanying the malady. The name dermatopolyneuritis, recently proposed by Thursfield and Patterson, seems more acceptable than any other yet suggested.

The clinical picture of this disease was first given to the American medical profession by Bilderback, of Portland, Oregon, who reported a series of cases before the Northwestern Pediatric Society, January, 1920. Since his contribution much attention has been aroused and many reports have been made from various parts of the country. Under the name erythredema H. Swift in 1914 reported certain typical cases which occurred in his practice in Australia. Since then Swift, Jefferys Wood, Snowball and Clubbe, and F. H. Cole, all Australian observers, have reported cases of this disease.

Weston chose the term "acrodynia" because he felt that there was a resemblance between this disease and an epidemic disease described early in the nineteenth century as "mal des pieds et des mains" by certain Frenchmen. As this disorder, then described, was apparently of an epidemic character and occurred only in adults, it seems hardly likely that it bears any relation to the disease we are now considering. (Parkes Weber suggests that these cases were probably community poisonings with arsenic.) Weston himself, however, in 1914 in a paper on pellagra includes a case which he designated pellagra-sine-pellagra, which was undoubtedly what he now calls acrodynia.

The case presented today is by no means illustrative of all the symptomatology of the condition, for it is a relatively mild manifestation. Therefore it will be well to take up symptoms one by one, to study them, and to look to other histories of our own and to the published records of other observers to amplify the picture.

Individual Symptoms.—*Cutaneous.*—Only a few of the cases present general involvement of the skin at any given time. The lesions show first usually on the chest and abdomen. They come as erythematous, fine, pin-point macules which tend to coalesce. Soon certain of these develop into papules, pinhead in size, but very slightly raised. The excessive secretion of perspiration influences the affected area to produce tiny miliaria-like vesicles. Drying and scratching, which is incessant, bring about branny desquamation and a staphylococcal infection, even to the degree of shallow furuncles. The rash appearing on the hands and feet may be the first sign of the malady; usually the cheeks are synchronously affected. It is more usual, however, for the involvement of the extremities to follow some weeks or even months after the first development of symptoms referable to irritation of the nervous system, such as hypotonus, posturing, and changes in temperament.

Dental.—The history of one patient shows that gingivitis as it occurs in the disease may be severe and, if improperly treated, lead to extreme deformity. The cause of her gingivitis was unrecognized, and on the assumption that the condition in this child of twenty months was a pyorrhea, excessive dental zeal led to an extensive curetment of the maxillary bone. There followed an invasion of the blood-stream by Streptococcus hemolyticus, with the later production of an osteomyelitis which ate away much of the acetabulum and of the head of the femur. An osteomyelitis also occurred in both maxillary bones and brought about sequestration and other damage which greatly marred the child's beauty.

Stomatitis and gingivitis are by no means constant manifestations of the disease. Although only about one-third of the cases exhibit one or both of them, gingivitis sometimes goes on to

exfoliation of the teeth. That shedding of the erupted deciduous teeth may take place while the unerupted teeth of the first set and the dental sacs of the second set remain undamaged is evidenced by the history of a boy seen fourteen years ago, who, during an attack in the early part of his second year, lost all of his temporary incisor teeth, but later on erupted the rest of the set in healthy condition. His permanent teeth are remarkable for hardness, size, and soundness.

Coincident with the height of the skin rash the mouth may suffer an ulcerative stomatitis, and there may also occur superficial ulcers and fissures in the skin at the corners of the eyes and of the mouth.

Fig. 105.—Postural peculiarity in child.

The Nervous System.—Paresthesia of extremities, pain, diminished cutaneous sensibilities, photophobia, diminished reflexes, dulness and apathy alternating with restlessness, irritability, peculiar position, cold hands, and feet are characteristic of all instances of this disease. The peculiar positions assumed by the child are especially noteworthy. The postures taken by one child differ quite markedly from those assumed by another. The commonest attitude is the knee-chest position with the legs drawn up. Sometimes the legs are twisted in awkward and unexpected ways. Another attitude quite commonly to be observed is one in which the child lies on its back with his hands over the face, and thighs fully flexed on the body, with the toes pointed over the shoulder. One child, resident in Lane Hospital

a number of years ago, seemed to find most joy in a position of this sort, but, in addition, most of the time it kept its head hyperextended so that the forehead was pressed against the bars of the crib. Sometimes this hyperextension assumed such a degree that the body was almost resting on the forehead. Such positions are more commonly seen during the intervals between the exacerbations of acute eruption. At the time of the eruption the hands and feet are apparently so painful that the children are constantly scratching the body, and they are, therefore, apt to assume the knee-chest position, which seems to give them ease. Apathy, dulness, and listlessness are marked whenever the child is left to himself, but as soon as he is interfered with, restlessness and irritability supervene. This is true in all the cases we have seen, but sometimes in the course of certain of them, usually the most severe, listless apathy becomes predominant. The reflexes of all the patients seriously affected are diminished, and at one time or another disappear. In no case that we have seen have any of the reflexes been exaggerated.

The Respiratory System.—The large number, but by no means most, of the reported cases have shown an upper respiratory tract infection. We have never been able to cultivate any organisms other than streptococcus, staphylococcus, and Micrococcus catarrhalis from the upper respiratory tract when such an infection was rife.

In some of the cases a persistent severe affection of the middle and larger bronchial tubes is a feature. This form of loose productive bronchitis has occurred only in severe cases. Among the cases that have come under our own observation no pneumonia in any of its forms has been encountered.

Digestive System.—As has already been said, more than half the children, among them all the less seriously afflicted, suffered from constipation. In 2 cases marked abdominal pain was a feature, but the more severely affected patients suffer from diarrhea. These are much the most difficult to deal with, as this symptom is persistent and resists the ordinary methods of treatment, although it seems to improve when thoroughly cooked and finely cut green vegetables are given in quantity.

Urinary System.—A number of the girl children at one time or another during the disease show the presence of pus in the urine, a condition which cleans up spontaneously as the general status improves.

The Onset.—The malady as we have encountered it and as it has appeared to other American, English, and Australian observers is a disease of late infancy and early childhood. The earliest signs are related to changes in the nervous system. Briefly, these can be summarized as a change in temperament characterized by irritability, restlessness, profuse sweating, disturbed sleep, and accompanied by anorexia, sometimes with acute abdominal pains and constipation, at others marked by the passage of loose stools. Persistent diarrhea may become aggravating, even alarming, if it produces as it sometimes does an extreme dehydration. This frequency of bowel evacuation seems to be aggravated by a milk diet and to be ameliorated by feeding in which the rations of green vegetables, fruits, and carbohydrates are generous.

The eruption on the skin follows shortly after the signs of nervous disturbance. It appears first on the body and face. Most often at this stage the feet and hands are symmetrically affected. They are swollen, sometimes slightly cyanotic, sometimes erythematous. As in the case of this child, the swelling of the digits may be such as superficially to resemble a dactylitis. Vesiculation and desquamation appear early on the body. The same processes as they occur on the extremities are usually, but not always, later-appearing phenomena. The itching of the skin is one of the early manifestations. In some instances it antedates the appearance of erythematous macules, the initial visible lesions of the skin. Coincident with the first cutaneous signs there may be analogous lesions in the mouth, on the lips, on the buccal mucous membrane, and especially on the gingival mucous membrane. In certain extreme cases the gingivitis is proliferative and the teeth are shed early.

Among the earliest signs are evidences of burning and itching of the hands and feet. The victim will constantly twist and

rub both hands and feet. Some of the patients fall asleep only when the extremities are being gently rubbed.

The **course of the disease** is marked by exacerbations and remissions. The duration varies. Mild seizures may go on to complete recovery within a few weeks. The severe cases, on the other hand, may run for months. In the most protracted of our

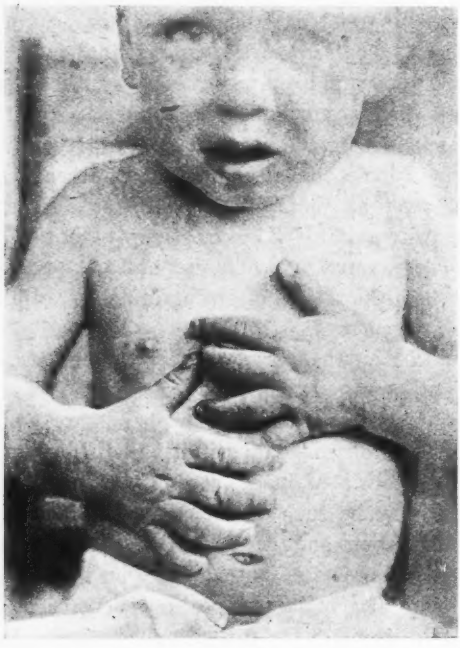

Fig. 106.—Hands showing dactylitis-like swelling of fingers and characteristic expression.

cases, complicated by a Streptococcus hemolyticus infection of the blood-stream with an osteomyelitis, the patient was affected for nearly two years.

The stages of exacerbation are marked by an increase in the itching eruption, augmented pains in extremities, and greater discomfort of hands and feet, together with an exaggeration of

the digestive disturbances, while restlessness and insomnia become more marked.

Of our 12 cases, 2 have died, 1 after an intercurrent attack of measles and 1 apparently from exhaustion as a result of the disease. Autopsies revealed only a general adenopathy. The glands were of moderate size except those of the retroperitoneal region. In this area the lymphatic glands were very large, varying in size up to the mass of a pigeon's egg. Unfortunately, in

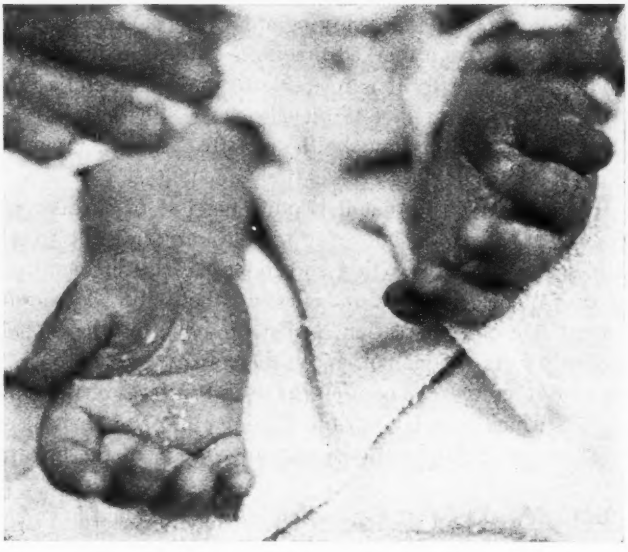

Fig. 107.—Hands showing palmar desquamation.

neither instance was examination of the central nervous system permitted, so that we were unable to compare the findings with those of Byfield, who found glial changes about the central canal of the cord and some staining peculiarities in certain of the anterior horn cells.

The **etiology** of this condition is still in question. Brown, of Toronto, thinks it the result of an infection which enters primarily through the nose and throat. Others have considered

it the result of a chronic intoxication following gastro-intestinal disturbances. Our own constant findings of a predominant proteolytic intestinal flora tends to make us sympathetic toward this view, though the evidence is by no means conclusive. McNeil has contended that the nervous symptoms indicate primary cerebral irritation. Goldberger has consistently classed the affection as a form of pellagra. That this is a warranted assumption seems improbable because pellagra is, for the most part, a disease of adults; it most often occurs in familiar groups and exhibits a well-marked geographic distribution. Unlike acrodynia, it shows a marked predilection to recur in the same individual and usually it is referable to previous dietetic error. Furthermore, against dietetic deficiency as an etiologic factor in this malady can be brought the fact that in all but a few of the cases the feeding has been entirely adequate.

It is certainly true that it is quite possible to mistake mild pellagra for acrodynia, but, even so, the former disease usually exhibits certain features that should be clearly distinguishing. The rash of pellagra reaches higher up the limbs. It shows a clear-cut line of demarcation, while acrodynial erythema fades out gently from desquamation, on fingers and toes, through an area of erythema, to be seen on the dorsal surfaces of the hands and feet, which merges first into a faint blush and then blends almost imperceptibly with the unchanged skin of the forearms and arms.

But a few cases that can be considered acrodynia have been reported from those areas in which pellagra is commonly found. Acrodynia patients are young, some breast fed; the others, for the most part, have received an entirely adequate ration.

The diminution in the reflexes and other evidence of peripheral neuritis has led some observers to search, so far without reward, for an etiologic factor that would bring the disorder into a group with beriberi and allied food factor deficiency disease.

In acrodynia, paresthesia together with pain and circulation changes in the extremities at once suggest that the pathology of the malady has much in common with or akin to the erythromelalgias and acroparesthesias of adults, but no one has been

able so far to bring any evidence that will substantiate the idea.

Treatment.—As the etiology of the condition is unknown it is obvious that treatment must be symptomatic. The fact is that most cases are self-limited, going on to speedy recovery. However, the annoying symptoms must be met by appropriate treatment, which includes rest in bed, fresh air, when possible, sunshine, and forced feeding. The results of stool examination indicate that carbohydrates, sugars, green vegetables, and fruits should be used in quantity. We have found in our own cases that the withdrawal of milk seems to accelerate the improvement, and that the return to milk feeding is followed by a rising of symptoms. When infections of the tonsils and sinuses are present, these must be treated appropriately.

Atropin sulphate has been useful in control of sweating. Mouth eruptions can be improved by a spray of zinc chlorid lotion and by scrupulous cleanliness. In some cases cod-liver oil was used with excellent effect. Chloral hydrate is useful when sleeplessness is persistent. Calamine lotion is sometimes suggested, freely and frequently applied to prevent the itching. It is of value, as it seems to hasten healing. However, a dusting-powder containing phenol, calomel, and light carbonate of magnesia together with zinc stearate is superior. This powder is especially valuable when the skin eruption is in the vesicular stage.

Appropriate treatment can be summed up as including local applications to the skin, sometimes forced feeding, rest, quiet, sunlight, cod-liver oil, and a liberal diet in which carbohydrates and green vegetables predominate.

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ACUTE YELLOW ATROPHY ASSOCIATED WITH HYPERTHYROIDISM*

THE liver is susceptible to serious injury by a variety of chemical substances, among the best known of which are chloroform, phosphorus, and trinitrotoluol. Pregnancy is complicated sometimes by extensive liver destruction produced by an unknown toxic agent. The underlying factors in the production of the more chronic disorders of the liver, classified as the cirrhoses, are obscure. From clinical and experimental data it is clear that the liver parenchyma is readily damaged in a variety of ways. On the other hand, there is probably no other organ of the body which has greater reparative power, compensation being rapidly restored unless the amount of parenchymatous tissue destroyed is too extensive.

Degenerative changes produced by toxic substances are not limited to the liver. Diphtheria toxin may cause profound changes in the heart, kidneys, adrenals, spleen, and nerves, as well as in the liver. Chloroform may produce serious injury to the liver parenchyma and heart muscle.

Recent studies by Fahr,[1] 1916, called attention to pathologic changes in the heart muscle in hyperthyroidism, which probably had been previously overlooked. These findings consisted of interstitial myocarditis with round-cell infiltration between muscle-fibers and around vessels plus fragmentation and destruction of muscle-fibers. Goodpasture,[2] 1921, in a detailed report of 2 cases of hyperthyroidism with myocarditis and auricular

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fibrillation, resulting in death, found myocardial necrosis to be extensive and diffuse in one and limited and focal in the other. The pathologic picture in the case with extensive and diffuse necrosis was so striking that such changes in the heart must be considered as extremely rare in hyperthyroidism. The history in this case of sudden death with such extensive necrosis, without histologic evidence of any attempt at repair, suggested that the lesions were terminal. In the other case the lesions in ventricle and auricle were focal, involving very small areas, with evidence of attempts at repair suggesting a process of longer duration.

Experimental studies on rabbits by Goodpasture,[3] 1921, showed that slight but definite lesions of the myocardium could be produced by large doses of dried thyroid gland and thyroxin. When combined with light chloroform anesthesia the lesions in the heart were striking and wide-spread, although usually no central necrosis was noted in the liver. This author suggested that the thyrotoxic heart was susceptible to the action of chloroform when given as an anesthetic in an amount insufficient to produce serious injury to the liver.

Hashimoto,[4] 1921, using albino rats in a histologic study of the heart in experimental hyperthyroidism, was able to reproduce the lesions described clinically by Fahr. Hashimoto also described the lesions found in other organs of the body, and inasmuch as the data on the liver are of interest in our report we shall quote verbatim:

"Liver, spleen, lungs, kidneys, suprarenal glands, and pancreas were examined microscopically. The material was obtained from 14 normal albino rats, used as control (10 males and 4 females), 12 that had been killed after having received toxic doses of thyroid, 9 that were found dead in the course of thyroid administration, and 10 that were killed after having received prolonged administration of non-toxic doses of thyroid. The findings in this examination will be briefly described.

"*Liver.*—Frequently parasitic cysts were found in the liver of albino rats employed for these experiments. It is evident, however, that the presence of these cysts for the most part has nothing to do with the function of the liver, for there is usually no histologic change in the areas adjoining the cysts, except the rare occurrence of a slight proliferation of connective tissue. It is quite possible that the infiltration of a few small round cells about the gall-

ducts or blood-vessels in the capsules of Glisson, found in some 36 per cent. of the normal controls, are not due to the parasitic cysts, inasmuch as such infiltrated areas were situated anywhere in the liver, quite independent of these cysts. Furthermore, there appeared to be no correlation between either the occurrence or the severity of such changes and the number of the parasitic cysts.

"Marked histologic changes resulting from thyroid feeding are shown in the parenchymatous degeneration, which was observed in quite a large number of animals receiving toxic doses of thyroid, whether killed at early stages in the experiment (50 per cent.) or found dead at later periods (73 per cent.). The liver cells encircling the efferent veins showed various stages of disintegration varying from simple fatty degeneration to necrosis. Occasionally such changes were present throughout the lobules, but were never entirely confined to the zone adjoining the portal veins, as observed in eclampsia gravidarum.

"In addition to the parenchymatous degenration evidences of chronic passive congestion and its results were seen in the livers of the animals dying later in the course of the thyroid administration (71 per cent.). The efferent veins in the center of the lobules and the adjacent capillaries were greatly distended with blood. The liver cells were collapsed and occasionally even destroyed, the framework alone remaining. It was frequently seen that this framework was hypertrophied and accompanied by marked proliferation of Kupffer's stellate cells.

"On the other hand, in the peripheral zone of the lobules showing degenerative changes in the center there frequently occurred hyperplasia of the liver cells, presumably the repairing process. There appeared a large number of mitiotic figures or double nuclei in the cells, and many young cells with pale and clear protoplasm and large nuclei. The occurrence of hyperplasia of liver cells without previous disintegration of the same cells was, however, very rare.

"With regard to the relation existing between the various histologic changes above described and the myocarditic lesions, it is of interest to note that the evidences of severe chronic passive congestion of the liver were found in the animals that showed severe myocarditic lesions; whereas in the animals showing only slight or no myocarditic lesions the liver was not congested, even when a fair degree of degenerative change was evident in the liver cells."

REPORT OF CASES

Case I.—U. C. H., No. 12,563. History: Male, white, age thirty-nine, was first admitted to the Medical Ward October 27, 1921, for treatment of hyperthyroidism.

Family History.—Essentially negative.

Past History.—Birthplace Ohio. He had spent two years in the Philippines in army service and had resided in California for eighteen years. Occupation, painter and farmer. He had been "moderately leaded" twice, previous to twelve years be-

fore entry. Previous diseases consisted of pertussis as a child, measles, malaria, tropical ulcers on both knees, and intermittent dysentery with mucoid stools between the ages of eighteen and twenty years while in the Philippines. There was a suggestive duodenal ulcer history. Neisser infection with cystitis at eighteen years. His habits had been good except for excessive use of tea. He lived in the country (goitrous district) and drank large quantities of spring-water.

Present Illness.—The patient considered himself well except for occasional abdominal cramps, constipation, and epigastric pain until 1918 (three years before entry), when he had influenza. Thereafter he never regained his strength. Acute symptoms of hyperthyroidism came on five months before entry, when he had sudden onset of marked nervousness, palpitation, trembling of hands and feet, weakness of the knees and profuse perspiration. He felt excessively warm. He gave up work, but did not consult a physician until two months before entry, when a diagnosis of hyperthyroidism was made, although no thyroid tumor was found. Three weeks before entry a tumor was first noticed in the neck, varying in size, and was never large. During the five months previous to entry the symptoms showed very little change except that his appetite became "ravenous" and his weight increased 11 pounds. During the three weeks previous to entry there had been a further increase in symptoms, his appetite diminished, and he lost about 10 pounds in weight. He complained of constipation throughout the present illness. There had been one attack of rapid beating of the heart at night, with choking sensations in the throat and chest (possibly due to paroxysmal auricular tachycardia or fibrillation). Slight edema of the ankles had been noted at times during the present illness. He complained of nocturia (six to eight) for a year, with urgency for a few weeks. No central nervous system symptoms.

Physical Examination.—The patient was a well-developed man of his stated years, spare of build, fairly well nourished, co-operative, and impulsive in speech and actions. His gait was normal. On standing there was a tremor of the legs. The skin was warm, moist, and of fine texture. The face, hands, and ears

were slightly cyanosed. Hair sparse. There were a few pea-sized cervical and inguinal glands. The eyes showed a coarse tremor of the lids when closed and some puffiness around the lids, but there were no other eye signs usually associated with exophthalmic goiter. Extrinsic muscles of the eyes were normal. The pupils were equal, regular, and reacted normally. The fundi were normal. The ears and nose were normal. The teeth showed some pyorrhea and retraction of the gum margins. The tongue showed a marked tremor. A small amount of purulent material was expressed from moderate-sized tonsils. The thyroid gland was moderately enlarged, the right lobe being larger than the left. The surface was smooth. There was a systolic thrill and bruit over both lobes. No apparent substernal extension. There was no increase in the substernal dulness and no enlargement of the spleen. The chest was symmetric except for a deformity of the left clavicle due to old trauma. The veins were dilated over the right chest anteriorly. Expansion was good. Breathing was exaggerated over the right upper and middle lobes, with a few inspiratory sonorous râles. Otherwise the lungs were within normal limits. The heart was enlarged to the left and downward, the action was regular, rate 120, increasing to 172 on slight exertion. The sounds were loud, A^2 greater than P^2. There was a faint systolic murmur over the base not widely transmitted. There was a diffuse pulsation over the precordium and a systolic thrill at the apex. Arterial pulsations were visible in the neck, groins, and abdomen. A capillary pulse was present. The head bobbed with systole. Blood-pressure: Systolic 120 and diastolic 65 mm. Hg. The abdomen was within normal limits. No organs were felt. Area of liver dulness normal. Spine normal. There was a marked fine tremor of the hands and legs, which was increased on effort. The finger-nails were curved. Genitalia were normal. The reflexes were equal and active. No pathologic reflexes.

Laboratory Findings.—The urine was normal except for 4 to 5 pus-cells per h. d. f. with mucus. The blood showed 80 per cent. hemoglobin (acid-hematin method); red blood-cells 3,900,000; white blood-cells 6600. Differential count: Polymor-

phonuclear neutrophils, 62 per cent.; small mononuclears, 22 per cent.; large mononuclears, 16 per cent. Red cells appeared normal. The blood Wassermann reaction was negative. The sputum was essentially negative. The stool was normal. No occult blood, parasites, or ova. The blood-sugar curve began at 0.095, rose to 0.198 at the end of one-half hour; 0.259 at the end of one hour, and fell to 0.177 at the end of two hours. The urine was negative for sugar at the beginning of the test and at the end of one-half hour. At the end of one hour 1.5 per cent. of sugar (0.8 gm.) and at the end of two hours 2.35 per cent. of sugar (2.67 gm.) was found in the urine. The basal metabolism was 78.8 per cent. above the theoretic normal. *x*-Ray findings of the lungs and heart were negative except for a straight left heart border. Electrocardiogram showed tachycardia (rate 105), prominent T waves in all leads. The temperature on admission was normal; the pulse varied from 100 to 120 and the respirations were from 20 to 25 per minute.

Clinical Course.—Two weeks after entry radium emanations, 10 bare glass tubes of 6.5 mc. (total), were inserted into the thyroid gland under local anesthesia without immediate reaction. Twelve days later there was a two-day rise in temperature to 39° C.; pulse to 140, with respirations unchanged. The throat was sore and hoarseness developed. The weight on entry was 60.6 kilos, gradually falling to 50 kilos when he was discharged, November 29th, one month after entry. The appetite gradually failed and he was finally sent home because of dissatisfaction with hospital diet and the conviction that home cooking would agree with him. Basal metabolic rate on discharge was 66 per cent. above the theoretic normal.

Summary.—A male of thirty-nine years, farmer, entered the medical ward on October 27, 1921, complaining of weakness for three years, following attack of influenza. Acute symptoms of hyperthyroidism had been present for three months and a thyroid tumor had been noted for three weeks with a further increase of symptoms. He entered the hospital complaining of nervousness, palpitation, tremor of hands and feet, weakness of the legs, increased perspiration, loss of weight, increased appe-

tite, polyuria, and thyroid tumor. The physical examination revealed severe hyperthyroidism with a vascular thyroid tumor of moderate size. There was no exophthalmos. The heart showed moderate enlargement with good compensation. The liver and spleen were not enlarged. Aside from the high percentage of large mononuclear cells, no evidence of thymic enlargement was obtained. The blood-sugar curve showed a decreased carbohydrate tolerance. The basal metabolic rate was markedly increased. There was a loss of 10.6 kilos in weight during the month in the hospital. Radium was inserted into the gland, with a probable slight reaction twelve days later. The patient left the hospital unimproved, to continue treatment at home and return in one month for further observation and treatment.

Diagnosis.—Marked hyperthyroidism with cardiac hypertrophy.

Second Entry.—On December 20, 1921, three weeks after discharge, the patient returned to the hospital. During the first two weeks after discharge his weight fell to 47 kilos, and his appetite remained poor. Then improvement began with an increase in strength, appetite, and weight. The nervousness and other symptoms remained about the same. He still complained of marked constipation. There had been some local throat symptoms from the radium reaction which were subsiding.

The physical examination was essentially as on the first entry. The weight was 51.2 kilos, the temperature was normal. The pulse was 120, respiration 25 per minute. The thyroid gland showed no change in size and there was a thrill and bruit over both lateral lobes. The heart showed no change, blood-pressure 130 systolic, 60 diastolic, with a sound heart to zero. A laryngeal examination showed a catarrhal laryngitis, with widening and thickening of arytenoids. Cords moved well.

Laboratory Findings.—The blood showed a slight secondary anemia. The urine was negative except for an occasional pus-cell and mucus. The stools were negative. The basal metabolic rate was 73.3 per cent. above the theoretic normal. *x*-Ray of the

chest showed the heart as before. There was a widening of the upper mediastinal shadow due either to thymus or substernal thyroid.

Clinical Course.—The patient remained on the medical ward for two weeks during which time there was marked improvement in the general condition. The pulse gradually fell from 130 to 100. The appetite improved, the nervousness and tremor diminished, and the weight rose from 51.2 to 54.4 kilos. On January 5, 1922 a bilateral partial lobectomy was done by Dr. W. I. Terry under gas and oxygen anesthesia. The condition of the patient during the operation was good. January 5th after the operation the patient was very restless. The temperature rose to 38.6° C. and pulse to 148. On the following day he remained restless and excitable. Ice-bag therapy was instituted and opium was given by suppositories.

January 7th: Pulse was down to 130. Condition was improved. He was much quieter and had a good appetite.

January 8th: Dressing was changed, clips removed, wound in good condition. Patient was more excitable than is usual after thyroid operations.

January 10th: Temperature was down to 37.4° C. The pulse varied from 100 to 120. He sat up part of the day, but appeared unusually nervous and excitable.

January 13th: Transferred to medical ward. During the past two days the temperature had gradually risen from 37° to 38.8° C. The pulse rose from 100 to 125, the respirations were increased from 22 to 32. The appetite was unusually good. No abnormal signs were found in the lungs. The wound was clear.

January 15th: There was general improvement. The temperature was gradually subsiding since January 13th. The pulse was down to 100, the respirations were 20. The appetite continued good.

January 16th: Appetite began to fail. Vomited once. Temperature, pulse, and respiration as on January 15th.

January 17th: Vomited three times, refused nourishment, complained of nausea. The temperature was 36.2° C.

January 18th: The vomiting continued. The vomitus consisted of small amounts of sour fluid occasionally streaked with blood. The temperature varied from 37° to 38° C. The pulse rose rapidly to 140 on slight exertion, the respirations remained at 22. The weight had fallen to 50 kilos. He slept poorly. There were frequent brief periods of perspiration and palpitation. He felt drowsy. The scleræ were noted as icteric. Nausea and vomiting continued during the day. The vomitus was small in amount and was occasionally blood tinged. Sight of blood nauseated him.

January 19th: There was definite jaundice. He complained of extreme weakness and palpitation. The temperature was 36 to 36.6, the pulse 140, and respirations 24. The blood showed Hg. 70 per cent. (acid hematin method); red blood-cells 4,200,000; white blood-cells 9500. Differential count: Polymorphonuclear neutrophils, 81 per cent.; small mononuclears, 17 per cent.; large mononuclears, 2 per cent. The vomiting was less during the day. The sight of food caused nausea. The liver dulness was diminished. The jaundice deepened. Bile was present in the urine. Leucin and tyrosin crystals could not be found.

January 20th: After a poor night the patient was restless and irrational. The pulse was regular, but at times could not be felt. Temperature was 35.4° C. (rectal). Respirations were increased to 35. Ventilation was full, simulating respirations seen in acidosis. There were irregular periods of apnea, but the respirations were never typically Cheyne-Stokes in type. He became semicomatose, the respiratory difficulty continued; the pulse became weak and thready and the temperature rose to 36.6° C. (rectal). There were convulsive movements of the extremities during the early morning hours. The jaundice was deepening. No leucin or tyrosin crystals were found in the urine. Death occurred at 10 A. M. January 20th after a sudden attack of dyspnea, cyanosis, and rapidly failing pulse.

An autopsy was performed two hours after death. The following anatomic diagnosis was recorded:

A. 22. 7: Hyperplastic goiter with chronic interstitial stru-

mitis; partial thyroidectomy with well-healed surgical incision. Diffuse cardiac hypertrophy. Hypertrophy of thymus. Prominent malpighian bodies in spleen. Acute yellow atrophy of the liver; generalized icterus. Chronic cholecystitis. Hypertrophy of lymph-nodes along common and hepatic ducts. Acute hyperemic splenic tumor. Parenchymatous degeneration of kidneys. Hydropericardium (slight). Emaciation.

Of special interest was the liver. At autopsy it weighed 1290 gm. Its surface was rather coarsely granular, of light brownish-red color. On section, there was obscuration of normal markings; it appeared of yellowish-brown opaque color on which background were numerous deeply hemorrhagic, irregularly outlined blotches varying from just visible to about 1 cm. in diameter. After fixation in Jore's solution the tissues also exhibited an irregular green discoloration due to the jaundice and also tiny translucent gray spots, apparently in the center of the lobules with opaque tissue about the portal regions.

Microscopic examination of the various viscera gave the following findings:

Heart.—Pericardium appears normal. The myocardium was studied in a number of sections and showed here and there moderate separation of the fibers by edema. One small focus of chronic fibrosis without any evidence of exudative cells in relation to it was seen. In one section a rather marked focus of perivascular lymphocytic infiltration was seen. The muscle-cells showed rather large numbers of cells with nuclei of normally large size. Nowhere in the sections examined was evidence of focal necrosis of myocardium observed.

The *thyroid* showed a marked irregular breaking up of its tissues by irregularly running bands of fibrous tissue, much the way that fibrous bands cut through an atrophically cirrhotic liver. In places bits of thyroid tissue appeared to be undergoing compression in a partly necrotic hyaline connective-tissue mass. The thyroid parenchyma occurred as ascini varying in size and shape, in part containing colloid staining normally. In major part, however, the ascini contained little or no colloid, but were filled with desquamated cells or papillary infoldings; again,

there was more or less diffuse overgrowth of thyroid cells, with little or no attempt at acinar formation. To one of the thyroid sections a small mass of typical thymus tissue was attached (Figs. 108, 109).

Thymus.—This organ preserved to a remarkable degree the structure of early life. It showed large lobulated masses of

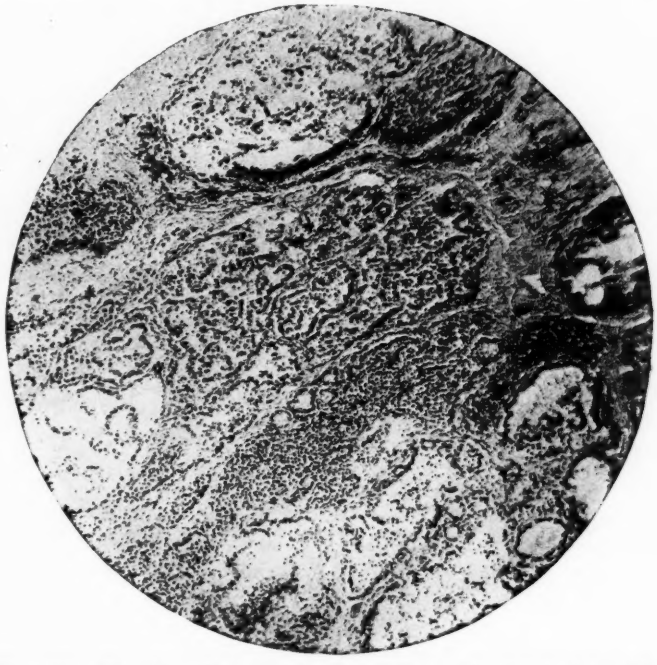

Fig. 108.—Thyroid. Hyperplastic toxic goiter with chronic interstitial strumitis.

lymphatic tissue. Scattered through it were numerous Hassel corpuscles, varying much in size, some being quite large and showing advanced stages of hyalinization, while an occasional small one appearing quite cellular. Scattered through the lymphatic structures were large mononuclear cells, often phagocytic, occurring singly as a rule, and possibly of endothelial origin.

Spleen.—The malpighian bodies varied much in size. In the larger ones there was often a relatively large so-called "germinal center." No evidence of degeneration was seen in them. The pulp was markedly suffused with blood, obscuring details, but no further abnormality was made out.

Fig. 109.—Thyroid. Hyperplastic toxic goiter with chronic interstitial strumitis.

Lymph-nodes taken from various regions, including those draining the liver, in general showed hypertrophy of the lymphocytic elements with large germinal centers and more or less hypertrophy of reticulo-endothelial elements.

Liver showed a remarkable picture. There was almost complete loss of architecture. The most conspicuous areas were those usually associated with the portal regions in which there

was a marked diffuse irregularly extending infiltration with lymphocytes and some plasma-cells. In the bile-ducts no exudate was observed. Within, but principally just beyond, these lymphocytic masses were irregular strands of liver cells separated by irregular groups of deeply pigmented cells, lymphocytes, remnants of necrotic cells, and scattered polymorphonuclear

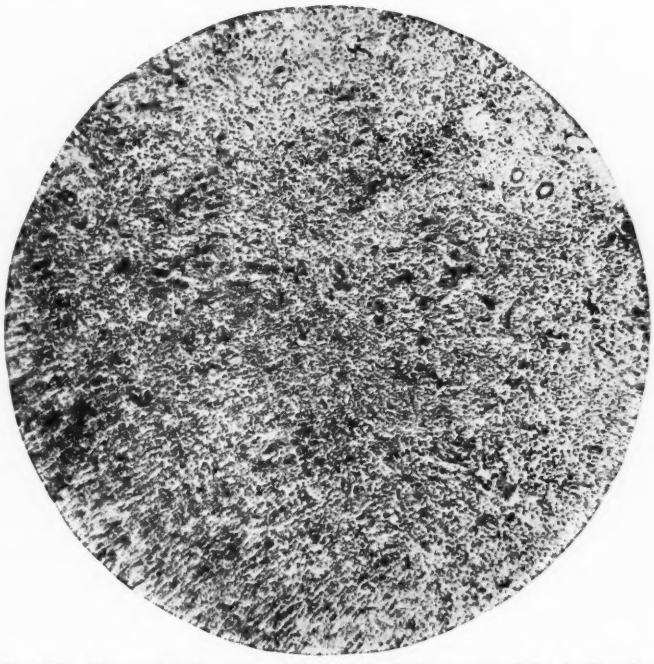

Fig. 110.—Liver, showing general destructive lesions and cellular infiltration.

neutrophils and eosinophils. In some areas hemorrhage occurred. A number of cells with extensively vacuolated cytoplasm were seen, but these appeared to have intact nuclei, and, indeed, at this stage of the process, it was impossible to make an estimate of the possible relative amount of nuclear damage in contrast to cytoplasmic; fibroblastic reaction was as yet not in evidence (Figs. 110, 111).

Lungs were negative.

Pancreas showed scattered foci of postmortem necrosis. Otherwise the organ was negative both as to glandular structures and islands of Langerhans.

Adrenals.—No abnormality was found.

Stomach appeared normal.

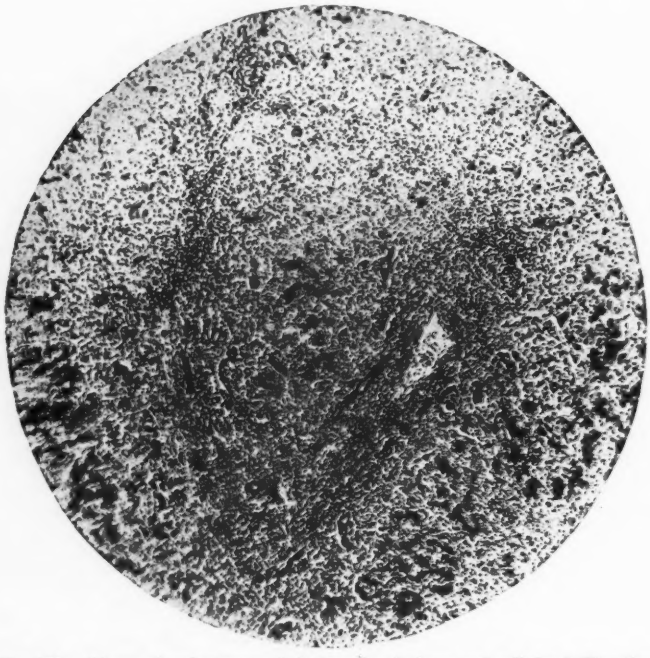

Fig. 111.—Liver, showing general destructive lesions and cellular infiltration.

Kidneys showed marked parenchymatous degeneration, also an occasional small focus of fibrosis and lymphocytic infiltration.

That the degree of liver atrophy, as judged by weight, was not great in this case, as compared with the often recorded weights, is obvious, but we feel justified in placing the case under the caption of acute yellow atrophy in view of the microscopic appearance as recorded above.

DISCUSSION

A certain degree of jaundice is occasionally observed in the terminal stages of thyrotoxicosis. The mechanism of the production of such jaundice has not been explained. It seems improbable that it has any relation to cardiac decompression and consequent passive congestion. It also seems improbable that it may be due to blood destruction, or at least we know of no evidence to indicate it. That the liver may be at fault, and by an extensive destruction analogous to acute yellow atrophy give the explanation, has not been recorded in human cases, so far as the writers are aware.

Our findings then bear directly on those of Hashimoto and his interesting results of liver alterations in association with thyroid feeding in rats which are cited above.

The etiology of acute yellow atrophy of the liver is also most obscure; toxic absorption from the gastro-intestinal canal has been surmised as the cause. Much discussion has taken place as to whether one is justified in making it a pathologic entity or whether various agents, destructive to the liver, notably phosphorus, chloroform, etc., should be given a place along with an unknown noxa, as producing analogous lesions differing only in degree. It might be argued that the lesions described in this case should be labeled "thyrotoxic degeneration" rather than acute yellow atrophy, but the writers feel that the latter term is perhaps the more conservative until such time as further experimental data are available to justify a separation. Such experimentation is being undertaken by us.

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